

SAFETY CONSIDERATIONS IN ONCOLOGY PHARMACY

Special Edition • Fall 2011



Promoting safety in the oncology pharmacy

Environmental contamination with cytostatic drugs: past, present, future

Human factors: safety lessons for oncology pharmacy practice

Cytotoxics preparation: reduction of medication errors and enhancing capacity

Should monoclonal antibodies and their conjugates be considered occupational hazards

Obtaining insurance coverage for the use of closed systems in Japan

Common toxicities of oral anticancer agents: an overview

Safe dispensing of oral chemotherapy

True to the motto 'the comprehensive approach', Sandoz Oncology Injectables (former EBEWE) always strives to support the whole oncology profession, including both oncology pharmacists and haemato-oncologists.

One of the major initiatives is the International Oncology Meeting, which is organised every year in Salzburg, Austria, always focusing on a different special topic of interest. The 2011 meeting was organised in collaboration with the International Society of Oncology Pharmacy Practitioners.

Safe and user-friendly product presentations are very important especially for cytotoxic drugs. Cytotoxic agents are valuable substances in anticancer treatment, but have also hazardous potential for the people involved in the production, preparation and use of these substances. The overall topic for the meeting was hence set as 'Dimensions of Safety Considerations in Oncology Pharmacy Practice'. The panel of speakers included renowned pharmacists from Australia, Belgium, Canada, Japan, The Netherlands Singapore, UK, and USA. The presentations covered a wide range of topics, shedding light on all the different aspects of the safety topic.

Over 200 pharmacists from 44 nations participated in this very interesting meeting, which was combined with site tour of the production facility located in Unterach am Attersee, Austria.

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Contents

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- | | |
|---|--|
| <p>2 Promoting safety in the oncology pharmacy</p> <p>3 Environmental contamination with cytostatic drugs: past, present, future</p> <p>6 Human factors: safety lessons for oncology pharmacy practice</p> <p>9 Cytotoxics preparation: reduction of medication errors and enhancing capacity</p> | <p>13 Should monoclonal antibodies and their conjugates be considered occupational hazards</p> <p>17 Obtaining insurance coverage for the use of closed systems in Japan</p> <p>20 Common toxicities of oral anticancer agents: an overview</p> <p>24 Safe dispensing of oral chemotherapy</p> |
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Authors:

Dr Paul JM Sessink, Rachel E White, Dr Anthony C Easty, Sarah Mahmoud, David Leonard, Professor Ann Jacklin, Dr Thomas H Connor, Barbara A MacKenzie, Dr Shin-ichi Sugiura, Mika Asano, Dr Hiroshi Gohma, Dr Hirokazu Nakanishi, Dr Tohru Hashida, Dr Masahiro Okuda, Phebe Si, Alexandre Chan, Robert McLaughlan

Editorial Office:

Postbus 10001, BE-2400 Mol, Belgium
Tel: +32 474989572 - Fax: +32 14 583048
info@ppme.eu - www.ppme.eu

Publisher:

Lasia Tang - Lasia.tang@ppme.eu

Senior Executive Editor:

Esra Kurt, PhD - editor@ppme.eu

Science Editor:

Neil Goodman, PhD - ng@ppme.eu

Production Assistant:

Rachel Mortishire-Smith - support@ppme.eu

Science Assistant:

Gaynor Ward - science@ppme.eu

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Promoting safety in the oncology pharmacy

Welcome to this special edition on *Safety Considerations in Oncology Pharmacy*. All personnel involved in the handling and preparation of cytotoxic oncology therapies are at risk from contamination [1]. An awareness of the dangers of these cytotoxic drugs, which can include adverse effects such as cancer, foetal malformations, and foetal loss during pregnancy, even at a low level of exposure, must be at the forefront of everyone's mind [1]. This is true even before the preparation of the medication begins, because several studies have shown that contamination can already be present on the external surfaces of drug vials supplied directly from the pharmaceutical manufacturers to the hospital pharmacy [2, 3].

Once these vials are opened, then all surfaces within the working area may become contaminated and, from here, the cytotoxic contamination may spread throughout the hospital and beyond [4, 5].

Due to the enormous variety and number of potential sources of cytotoxic contamination, a concerted effort has been made over recent years to combat this danger through education and improved safety measures and guidelines.

In this special edition, we have brought together several experts in the field with the aim of providing essential information on the important safety issues that need to be considered by the entire oncology profession.

On pages 13–16, Dr Connor and Ms MacKenzie discuss the toxic potential that monoclonal antibodies may have in the workplace. Dr Sugiura et al. describe the steps taken by the Japanese Society of Hospital Pharmacists to combat occupational exposure, see pages 17–19.

Ms Si and Assistant Professor Chan evaluate the current recommendations for the management of the most commonly observed toxicities among patients using oral anticancer agents, see pages 20–23.

Finally, on pages 24–26, Mr McLauchlan describes specific safety measures that have been implemented in order to optimise both patient safety and care.

We hope that we succeed in our aim of this special edition and, as always, welcome your feedback and continued discussion. Please feel free to share your thoughts via email to editorial@ppme.eu.

References

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. Mason HJ, Morton J, Garfitt SJ, et al. Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. *Ann Occup Hyg.* 2003;47:681-5.
3. Favier B, Gilles L, Ardiet C, et al. External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. *J Oncol Pharm Pract.* 2003;9:15-20.
4. Sessink PJM, Boer KA, Scheefhals APH, et al. Occupational exposure to antineoplastic agents at several departments in a hospital: environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. *Int Arch Occup Environ Health.* 1992;64:105-12.
5. Crauste-Manciet S, Sessink PJM, Ferrari S, et al. Environmental contamination with cytotoxic drugs in health care using positive air pressure isolators. *Ann Occup Hyg.* 2005;49:619-28.



Dr Sessink relates an interesting tool that can be used to evaluate preparation techniques in hospital pharmacies by measuring the level of environmental cytotoxic drug contamination, see pages 3–5.

Ms White and Dr Easty introduce how the principles of psychology and engineering can be incorporated in order to understand the complex interactions between personnel and the oncology pharmacy, see pages 6–8. Ms Mahmoud et al. describe, on pages 9–12, how the increasing complexity of chemotherapy over the last decade has increased the potential for error, identifies several of these errors, and proposes which measures can be taken to prevent them.

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Environmental contamination with cytostatic drugs: past, present, future



Paul JM Sessink, PhD

Measuring environmental contamination with cytostatic drugs has become an interesting tool to evaluate preparation techniques in hospital pharmacies. A preliminary model is presented here demonstrating that environmental contamination lower than 0.1 ng/cm² is a safe reference value.

Introduction

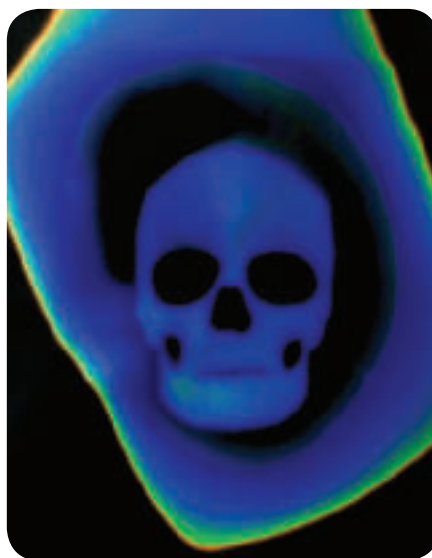
Cytostatic drugs have been used for many years in the treatment of cancer and non-neoplastic diseases. However, most cytostatic drugs are not selective in action and healthy cells are also damaged, which results in adverse health effects [1]. For healthcare workers such as pharmacists, pharmacy technicians, nurses, and medical doctors involved in the preparation and administration of these drugs, exposure may also cause adverse effects such as cancer, foetal malformations, and foetal loss during pregnancy even at low exposure levels [1].

To prevent exposure of healthcare workers to cytostatic drugs, biological safety cabinets and isolators have been installed, preparation and administration rooms are ventilated, devices and special mixing techniques are applied, and personal protective equipment (such as gloves, gowns, goggles, and special clothing) is used. All these precautions are well documented in guidelines and regulations set up by national authorities and (inter) national societies of healthcare professionals (pharmacist and nurses) and have the aim of offering maximum protection to the healthcare workers handling these toxic drugs [2, 3].

Monitoring

The first studies to evaluate exposure of healthcare workers to cytostatic drugs were published circa 1980 [4]. At that time, results demonstrated exposure of healthcare workers to cytostatic drugs based mainly on mutagenicity in urine (Ames assay) and the presence of chromosome aberrations and sister chroma-

tid exchanges in blood lymphocytes. The findings of these tests have resulted in worldwide regulations and guidelines [5]. Follow-up studies with these tests have shown a reduction in the exposure of healthcare workers to cytostatic drugs. Professionals involved in this issue were more or less leaning back, thinking that the problem was solved but in fact the opposite was the case. It was found that the tests did not show exposure of healthcare workers despite cyclophosphamide, a carcinogenic cytostatic drug, being detected in their urine. Due to lack of selectivity and sensitivity, these tests became less useful in the 1990s [4].



These new findings have resulted in the development of more sensitive methods for the analysis of individual cytostatic drugs or their metabolites mainly in urine [6-8]. In addition, one was more focused to find out the causes of the exposure [9]. This has resulted in the development of

so-called wipe tests to measure environmental contamination. With wipe tests, potential contaminated surfaces are pre-wetted and wiped with a tissue; the tissue is then analysed for the drugs to be monitored and, finally, the amount is calculated for the area wiped. By taking wipe samples, contaminated surfaces can be traced and ranked according to the level of contamination. The causes of the contamination can then be attempted to be elucidated. Wipe tests can be used to evaluate preparation and administration procedures, to test devices, and to check cleaning procedures.

Taking wipe samples has become very popular and, nowadays, many hospitals perform these tests on a frequent basis to evaluate their procedures and routines [10]. Most hospitals which perform these tests see a decline of the environmental contamination over time. In addition, the decline is not only observed for environmental contamination but also for the amounts of cytostatic drugs excreted in the urine of healthcare workers indicating a reduction of occupational exposure.

Developments

It is clear that a reduction of environmental contamination with cytostatic drugs will eventually result in a lower exposure of healthcare workers. Over the last decade, several developments have positively contributed to these results.

A tremendous reduction in environmental contamination has been achieved by the introduction of so-called closed-system transfer devices. With these systems,

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a leak-free transfer of drugs from vial to infusion bag, syringe or pump can be achieved. Although a number of companies have introduced these devices on the market, long-term clinical studies showing the effectiveness of the devices have not yet been published for the majority [11]. Objective criteria for a device to be considered as a closed-system transfer device are lacking; only a general definition is available, which indicates a closed system as one that mechanically prevents the transfer of environmental contaminants into the system and the escape of drugs or vapour out of the system [5]. Objective criteria should be set by authorities in collaboration with organisations of healthcare professionals such as American Society of Health-System Pharmacists and the International Society of Oncology Pharmacy Practitioners. It is a pity that, although these devices seem to be very effective in reducing environmental contamination, their use is only recommended and not obliged [1, 12].

Another improvement has been made by the pharmaceutical industry. The production of contained and sleeved vials has substantially reduced the outside contamination of drug vials [13]. However, there are still drugs on the market without such a protection or without information about the contamination on the outside of the vials. Therefore, it is important to stress that vials should only be touched when wearing gloves. The checking of vial contamination by independent authorities in combination with certification could further reduce contamination on the outside of drug vials. Acceptable levels or standards for vial contamination have to be set by authorities in collaboration with the pharmaceutical industry and hospital pharmacist organisations.

The third improvement is the increase of the awareness that handling cytostatic drugs implies a potential health hazard. Continuous education and training have contributed to inform healthcare workers about the risks when handling these drugs.

More recently, robots for the preparation of cytostatic drugs have been developed and some have been implemented in the hospital setting. However, clinical studies evaluating robots have yet to be published. Major concerns regarding environmental contamination and the exposure of healthcare workers are potential cross-contamination and spread of contamination inside the robot area and on the outside of prepared bags. This ultimately results in the transfer of contamination to administration areas. Independent validation studies need to be performed to investigate these potential concerns.

The Dutch approach

Nowadays, many hospitals take wipe samples and a question raised frequently is, 'Does the observed contamination result in exposure of the healthcare workers and, if so, what level of contamination is acceptable in terms of health risk?' These are legitimate questions because, over time, wipe samples continue to show contamination. More drugs will be prepared in the future due to more cancer patients, drug vials will still be contaminated on the outside, and detection limits of analytical methods will continue to be lowered due to new and more sensitive techniques.

Over the last 20 years, a lot of monitoring studies have been performed in The Netherlands. To evaluate procedures and to check contamination and exposure, the Dutch authorities have obliged hospitals to perform wipe tests

regularly. This has resulted in an enormous database in general showing a reduction of environmental contamination over time. In addition, excretion of cyclophosphamide has not been found indicating no measurable exposure to this drug. These findings have resulted in a debate about what is an acceptable level for environmental contamination in terms of health risk for healthcare workers.

Dutch healthcare professionals such as pharmacists, nurses, occupational hygienists, and toxicologists have discussed this issue for many years. A few years ago, a consensus was agreed on the approach of how to set an acceptable level of environmental contamination. A very pragmatic approach was followed based on the marker drug cyclophosphamide. The selection of cyclophosphamide was obvious: it is a highly toxic drug, resistant, with high skin permeability (skin exposure), and is frequently used and monitored (wipe and urine samples) due to sensitive analytical methods. In fact a worst-case scenario was followed (conservative approach). Based on the data set, 90% of the wipe samples show contamination levels $< 0.1 \text{ ng/cm}^2$ and 99% of the wipe samples show contamination levels $< 10 \text{ ng/cm}^2$. In addition, no positive urine samples were found at contamination levels $< 0.1 \text{ ng/cm}^2$ indicating no measurable exposure of the healthcare workers. This has resulted in the reference values 0.1 ng/cm^2 ('safe') and 10 ng/cm^2 ('not acceptable').

Table 1: Reference values for environmental contamination with cyclophosphamide (CP) in The Netherlands

	Strive risk level			Prohibitory risk level
Urine CP ($\mu\text{g}/24 \text{ h}$)	< 0.02	0.02–0.2	0.02–2	> 2
Contamination CP (ng/cm)	< 0.1	0.1–1	1.0–10	> 10
Actions	Monitoring once a year Evaluate after 4 years	Risk estimate Monitoring within 3–6 months Eventually followed by measures		Take measures Check by monitoring

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Based on these data, Dutch healthcare professionals have agreed on different types of actions to be performed depending on the levels of contamination found after wipe sampling (see Table 1). In addition, these data can also be linked to cancer risk estimates in terms of strive risk level and prohibitory risk level based on the analysis of cyclophosphamide in the urine of healthcare workers [14]. In the final 'traffic-light' model, it can easily be seen what levels of cyclophosphamide environmental contamination and urine excretion are acceptable and which actions need to be performed.

This approach is considered as a first step to indicate what can be considered as a 'safe' level for environmental contamination with cyclophosphamide. The approach will be evaluated after several years and will, if possible, be expanded to other cytostatic drugs.

Conclusion

Over the last thirty years, enormous steps have been set forward to reduce occupational exposure of healthcare workers to cytostatic drugs. The awareness has grown, closed-system transfer devices have been introduced, and cleaner vials have been produced. For the next decade, these developments need to be intensified in order to result in a further lowering of environmental contamination and consequent exposure of healthcare workers to these drugs. To follow and to

support these developments, the use of monitoring methods by taking and analysing wipe and urine sample are a must and will remain a permanent tool for measuring contamination and exposure at healthcare sites.

Author

Paul JM Sessink, PhD
Exposure Control Sweden AB
17 Klövervägen
SE-47537 Bohus-Björkö, Sweden

References

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No 2004-165.
2. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63: 1172-93.
3. ISOPP Standards of Practice. *J Oncol Pharm Pract.* 2007;13(Supplement):1-81.
4. Sessink PJM, Bos RP. Drugs hazardous to healthcare workers. *Drug Saf.* 1999;20(4):3 47-59.
5. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990;47(5):1033-49.
6. Turci R, Sottani C, Spagnoli G, Minoia C. Biological and environmental monitoring of hospital personnel exposed to antineoplastic agents: a review of analytical methods. *J Chromatogr B Biomed Sci Appl.* 2003;789(2):169-209.
7. Sessink PJM, Scholtes MM, Anzion RBM, Bos RP. Determination of cyclophosphamide in urine by gas chromatography-mass spectrometry. *J Chromatogr.* 1993;616(2):333-7.
8. Pethran A, Schierl R, Hauff K, Grimm CH, Boos KS, Nowak D. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations. *Int Arch Occup Environ Health.* 2003; 76(1):5-10.
9. Sessink PJM, van de Kerkhof MCA, Anzion RBM, Noordhoek J, Bos RP. Environmental contamination and assessment of exposure to antineoplastic agents by detection of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch Environ Health.* 1994;49(3):165-9.
10. Connor TH, Anderson RW, Sessink PJM, Broadfield L, Power LA. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm.* 1999;56(4):1427-32.
11. Sessink PJM, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract.* 2010;17(1):39-48.
12. USP <797> Guidebook to pharmaceutical compounding – sterile preparations. Available from: www.usp.org/products/797Guidebook
13. Connor TH, Sessink PJM, Harrison BR, Pretty JR, Peters BG, Alfaro RM, et al. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. *Am J Health Syst Pharm.* 2005;62(5):475-84.
14. Sessink PJM, Kroese ED, van Kranen HJBos RP. Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide. *Int Arch Occup Environ Health.* 1995;67(5):317-23.

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Human factors: safety lessons for oncology pharmacy practice



Rachel E White, MA (Psych)

Anthony C Easty, PhD, PEng, CCE

Human factors is a discipline aimed at reducing human error through changes to the systems in which people work. This article presents an analysis of a chemotherapy compounding error, and makes recommendations for how to incorporate human factors into oncology pharmacy practice.

Introduction

Oncology pharmacists play a critical role in ensuring that cancer chemotherapy is prepared in a safe and efficient manner. Pharmacies are constantly working to address challenges such as sterility and expiration, dosing accuracy, and protection from hazardous exposure, while at the same time facing rapid increases in production requirements and staffing constraints [1]. Creating and maintaining safe systems under such circumstances is therefore a growing challenge.

What is 'human factors'?

Human factors is a discipline incorporating principles of psychology and engineering into understanding and designing the interactions between people and the complex systems in which they live and work. One of the aims of human factors is to reduce the occurrence and impact of human error through an acceptance of humans' physical, cognitive and social capabilities and limitations. Rather than expecting humans to improve upon their innate abilities, changes to the system in which humans work are encouraged [2]. For example, if nurses repeatedly make programming mistakes on an infusion pump, the common response might be to send them on training, to give them frequent reminders, or to implement policies requiring them to double-check pump settings before initiating an infusion. In contrast, the human factors approach might be to change the design of the programming sequence on the pump's user interface so that the correct sequence is the most intuitive option.

High-risk industries such as aviation, nuclear power generation, and transportation have been employing human factors techniques to improve safety since the middle of the 20th century. However, concepts of human factors are relatively new to healthcare, and are only in the last decade gaining momentum. Like other areas of healthcare, oncology pharmacy practice is complex and high-risk for both patients and staff. Applying human factors principles to this area of healthcare is therefore a natural extension of the field.

and preventing adverse events in oncology pharmacy practice.

In 2006, a two year-old American girl died as a result of receiving an incorrectly compounded chemotherapy solution [3, 4]. A pharmacy technician made the base solution for the chemotherapy by manually compounding full strength 23.4% sodium chloride instead of using 0.9% solution. The pharmacist responsible for checking the final prepared product failed to detect the error and the child died from hypernatraemia as a result.



Unfortunately, this case had tragic consequences for both the family and the pharmacist. The family was devastated by the loss of their child. The life of the pharmacist, who intended no harm, was also forever changed. As a direct result of the error, he had his licence permanently revoked and was convicted of involuntary manslaughter. He spent six months in prison, six months in home confinement with electronic monitoring, three years in probation and 400 hours in community service. He also had to pay a fine of US\$5,000 and court costs [3].

To err is human

The technician made a mistake by compounding highly concentrated saline. The pharmacist failed to detect the mistake. The oft quoted phrase, 'to err is human' highlights that it is an inevitable part of human nature to make mistakes. Even the most experienced practitioners make mistakes, and the same set of circumstances can lead to errors being repeated by

A doubly devastating chemotherapy preparation error

A recent case of a tragic chemotherapy preparation error can be used to shed light on the role that human factors can play in understanding, responding to,

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multiple individuals [5]. An acceptance and expectation that humans will err is an essential component of a safe system [3]. In this light, and given that no harm was intended, the criminal prosecution of this pharmacist was highly inappropriate and counterproductive to the patient safety movement [3]. Though disturbing, this extreme response to the natural phenomenon of human error in this case is thankfully relatively uncommon.

Fatigue

The pharmacist had worked an evening shift until 23:30 the night before, and because the unit was short-staffed, he was asked to come in again in at 10:00 the next morning [6]. Research has shown consistently that humans are more likely to err when they have not had enough sleep, and that tasks requiring vigilance are especially at risk for error [7]. Checking large quantities of drug preparations, as the pharmacist was doing that morning, is a vigilance task. The timing of his shifts was therefore far from ideal and may have contributed to his failure to notice the compounding error.

Stress and efficiency pressure

The night before the incident, the electronic systems in the pharmacy had failed. When the pharmacist arrived in the morning, the unit was understaffed and there was a significant backlog of prescriptions as well as large stacks of duplicate labels and materials to deal with. He was motivated to clear this backlog as quickly as possible so that medications could be delivered to patients on schedule [6]. With these pressures, he did not have time for normal work breaks [3]. Also, that morning a chemotherapy nurse called the pharmacy to ask for the child's chemotherapy even though it was not required until the afternoon, so additional pressure was being applied to the pharmacist to work

quickly and efficiently, especially on this particular prescription [3].

Research has established that regular rest breaks are important for mitigating risk in work environments [8]. Further, task overload and time pressure have been shown to reduce human performance because of their impact on attention and working memory. As a result, people under stress tend to have simpler decision strategies, use recogni-

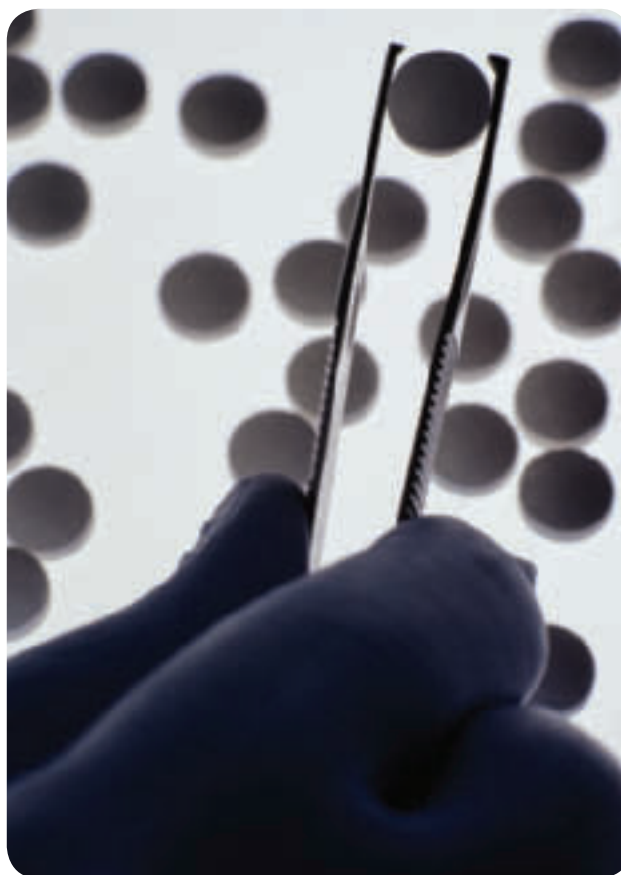
cluttered, as it often was. The backlog of orders contributed to multiple medications and materials being in a large pile [6]. The presence of 23.4% saline in the pile would not have been unusual because at this paediatric hospital, very low-fluid volume injections with highly concentrated saline were commonplace [6].

The collocation of multiple materials within mixing and checking areas has been identified as a serious safety hazard in research on chemotherapy safety [10], as well as in analyses of other adverse events [11]. If the checking table had been more organised, the pharmacist may have had a better opportunity to detect the error. For example, if each final prepared product had been placed in a single bin with its associated labels and/or medication order, empty vials and containers, the pharmacist would have been able to see that the wrong saline solution had been used.

Human error-checking

'Double-checks' or 'independent double-checks' processes, where a second individual verifies the work performed by the first, are common in healthcare, especially in pharmacy practice. The pharmacist in this case performed a check of the technician's work, but he failed to detect the error she had made.

Research on error-checking has consistently shown that no check performed by humans is 100% reliable. Human error detection has been shown to fail 5–20% of the time [3]. In fact, one study of independent double-checking of chemotherapy showed that depending on the specific approach to double-checking and the error type in question, checking failed to identify errors 10% to 100% of the time [12]. Exploratory research on chemotherapy safety in Canada has also found that certain combinations of mixing and checking approaches can effectively hide errors, making their detection almost



tional rather than analytical decision approaches and have restricted ability to gather information [9]. The pharmacist in this case was overloaded and under time pressure, and did not take breaks, so it is plausible that these circumstances may have played a role in his failure to detect the error.

Organisation of materials and work processes

The day of the error, the checking table in the IV compounding area was very

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impossible [10]. Error-checking is important because it catches some errors, but it cannot be relied upon entirely.

How can the human factors issues in this case be addressed?

This case is an example of how the system in which a person works can lead to human error. In hindsight, it is not difficult to imagine another individual in these circumstances making the same mistake. The following recommendations have the potential to reduce the impact of human error in an environment like the one described in this case:

- *To err is human.* Accept that errors are natural. Encourage a culture where errors are openly reported and discussed. Implement an electronic reporting system, and a process for systematically responding to errors. Support staff if they are ever unfortunate enough to be involved in an error. Look for changes that can be made to the system rather than to the people who work within it.
- *Fatigue.* Implement policies limiting the duration of work shifts and ensure a minimum amount of time between shifts. Encourage or mandate regular breaks. Ensure staffing is sufficient to make these policies achievable.
- *Stress and efficiency pressure.* Work to keep staffing levels consistent with changes in production levels. Ensure that safety-critical tasks are done in quiet and interruption-free zones. Manage the expectations of the departments serviced by the pharmacy by providing regular updates on expected production times.
- *Organisation of materials and work processes.* Ensure that the pharmacy follows the International Society of Oncology Pharmacy Practitioners standard of one mix at a time [13]. Keep production and checking areas tidy and organised, with materials for a single mix together, and separate from other mixes.
- *Human error-checking.* Know the limitations of human error-checking and build in other safety nets. Ensure that all the information needed to identify all possible errors is available to the person conducting the check.

Incorporating human factors into oncology pharmacy practice

The above recommendations are based on factors involved in a single case. Other safety issues in oncology pharmacy practice exist, many of which may not yet have led to a specific error in a given environment. Additional steps can be taken to proactively address human factors and safety issues:

- Read more about human factors [2, 5, 14, 16].
- Find and collaborate with human factors professionals in your community.
- Go on informal walkabouts and observe actual (not expected) practices. Look for opportunities where errors could occur.
- Conduct Healthcare Failure Mode and Effect Analysis [17] to identify hazards before they lead to an error.
- When incidents or near-misses occur, conduct root cause analyses [15].
- Collaborate in interdisciplinary teams to identify systems solutions to identified problems. Look beyond policies and training and towards changes to processes and designs that make it easy to do the right thing and hard or impossible to do the wrong thing.

Human factors is more of a mindset than a set of strict guidelines. There are many resources for healthcare professionals to learn to apply this mindset to their work. Although it will never be possible to eliminate human error from the very human-driven processes in health care, it is our hope that tragic errors such as the one described here will become things of the past, and that staff involved in errors will always be given the support they deserve.

Authors

Rachel E White, MA (Psych)
Human Factors Specialist

Anthony C Easty, PhD, PEng, CCE
Senior Scientist

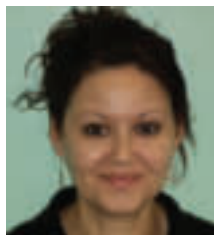
University Health Network
Centre for Global eHealth Innovation
4/F, R Fraser Elliot Building
190 Elizabeth Street
Toronto, Ontario, M5G 2C4, Canada

References

1. Summerhayes M. The impact of workload changes and staff availability on IV chemotherapy services. *J Oncol Pharm Pract.* 2003;9(4):123-8.
2. Gosbee J. Human factors engineering and patient safety. *Qual Saf Health Care.* 2002 Dec;11(4):352-4.
3. ISMP. Ohio government plays Whack-a-Mole with pharmacist. *Nurse Advise-ERR.* 2009.
4. Cohen MR. An injustice has been done: jail time given to pharmacist who made an error. *Institute for Safe Medication Practices.* 2009 Aug 21.
5. Reason J. Human error: models and management. *BMJ.* 2000 Mar 18;320(7237):768-70.
6. Pharmacy OneSource, editor. The Emily Jerry story. Online webinar; 2011 Jul 27.
7. Dinges D. An overview of sleepiness and accidents. *J Sleep Res.* 1995;4(Suppl 2):4-14.
8. Tucker P, Folkard S, Macdonald I. Rest breaks and accident risk. *The Lancet.* 2003;361(9358):680. doi: 10.1016/S0140-6736(03)12566-4.
9. Klein G. The effect of acute stressors on decision making. In: Driskell JS, E, editor. *Stress and human performance: Lawrence Erlbaum Associates, Inc.; 1996. p. 49-88.*
10. Health Technology Safety Research Team. *Improving the safety of ambulatory intravenous chemotherapy in Canada: Full study report and recommendations.* Toronto: University Health Network. 2011 Jan 14.
11. ISMP. *Safe practices in pharmacy compounding areas. Medication Safety Alert! Acute Care Edition.* 2011 Jun 2.
12. White RE, Trbovich PL, Easty AC, Savage P, Trip K, Hyland S. Checking it twice: an evaluation of checklists for detecting medication errors at the bedside using a chemotherapy model. *Qual Saf Health Care.* 2010 Dec;19(6):562-7.
13. International Society of Oncology Pharmacy Practice. *ISOPP Standards of Practice.* *J Oncol Pharm Pract.* 2007;13:1-81.
14. Reason J. Understanding adverse events: human factors. *Qual Health Care.* 1995 Jun;4(2):80-9.
15. Canadian Patient Safety Institute. *Canadian root cause analysis framework: A tool for identifying and addressing root causes of critical incidents in healthcare.* 2006 [cited 2011 August 10]. Available from: www.patientsafetyinstitute.ca/English/tools/Resources/rca/Documents/March%202006%20RCA%20Workbook.pdf
16. Vicente K. *The human factor: revolutionizing the way we live with technology.* Toronto: Vintage Canada; 2004.
17. United States Department of Veteran Affairs. *The basics of healthcare failure mode and effect analysis.* 2001.

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Cytotoxics preparation: reduction of medication errors and enhancing capacity



Sarah Mahmoud
BPharm (Hons)



David Leonard
BPharm



Professor Ann Jacklin
MPharmS

Over the last 10 years there has been an increase in cancer survival rates, increases in the complexity of regimens including the use of gene therapy and increases in the number of patients being treated in clinical trials. As a result of all of this, there is escalated pressure at all points of the chemotherapy process right through from prescribing to administration of the drugs. This could potentially result in an increased risk of errors occurring at some point in the process. This article seeks to identify some of these risks and discusses ways that Imperial College Healthcare NHS Trust (ICHNT) has tried to address them.

The Trust

Hammersmith Hospitals merged with St Mary's Hospital in 2008 to become Imperial College Healthcare NHS Trust, one of the UK's first Academic Health Science centres. ICHNT provides cancer treatment to around 600 new oncology

An increase in the complexity of chemotherapy over the last 10 years has increased pressure on all parts of the chemotherapy service and the potential for error. This article seeks to identify some of these errors and discusses measures to prevent them and ways to address capacity issues.

and haematology patients every year at the cancer centre for the North West London Cancer Network.

Haematology is based at the Hammersmith site, with three 16-bedded inpatient wards, and a large day unit treating lymphoma, acute and chronic leukaemic and myeloma patients. Hammersmith is also a Joint Accreditation Committee–ISCT and EBMT (JACIE) accredited Bone Marrow Transplantation centre.

Oncology patients are treated with chemotherapy on an outpatient basis at all three ICHNT sites: Charing Cross, Hammersmith and St Mary's. There are two 26-bedded oncology inpatient wards at Charing Cross. ICHNT treats all the major solid tumours (breast, colon, rectum, head and neck, neuro-oncology, skin, thyroid, upper GI urological, gynaecological, hepatobiliary) as well as a number of rarer cancers, e.g. gestational trophoblastic disease.

The St Mary's site also provides a shared care paediatric oncology service with Great Ormond Street Hospital and paediatric bone marrow transplants. We have licensed aseptic units at the Charing Cross and Hammersmith sites that are responsible for the provision of all chemotherapy for the three sites.

Medication errors in chemotherapy

Over 200,000 patient safety incidents were reported by National Health Service staff in England and Wales between 2003 and 2008. Of these reports, nearly 5,000 involved anticancer medications [1]. A review of these incidents showed that 23% of incidents occurred during

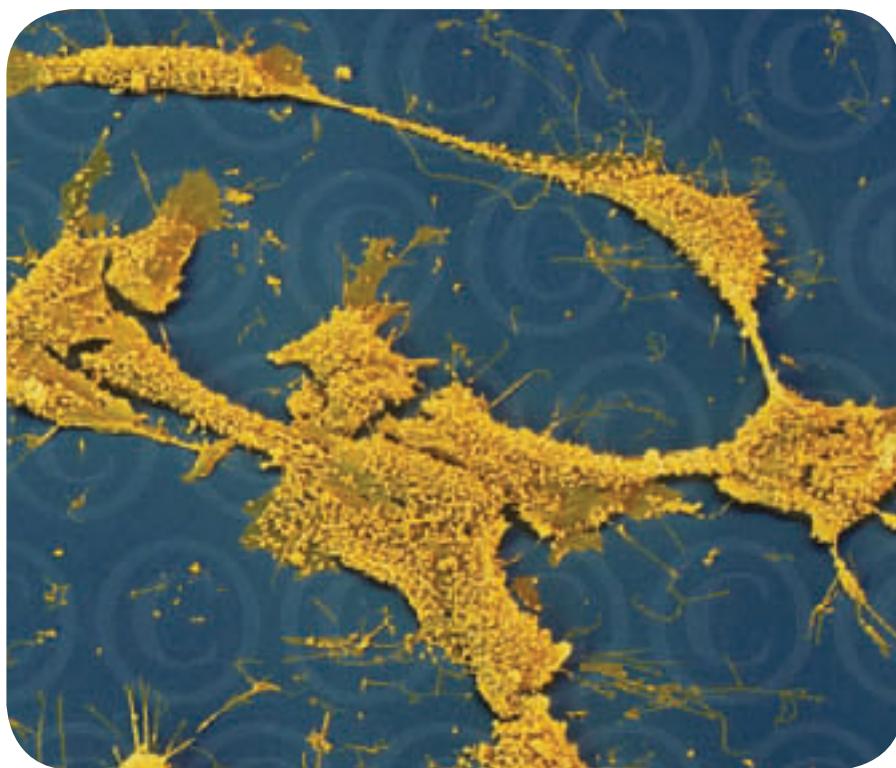
the prescribing process and 26% during the preparation process. However, the main area for harm was during the administration process (43%).

Measures to reduce errors in anticancer medication are therefore essential to reduce the risk of harm to patients. Several other reports in the UK have also highlighted the need for enhanced risk-management in the delivery of anticancer medicine, e.g. *National Confidential Enquiry into Patient Outcomes and Death*, for systemic anticancer treatment mentioned that many of the prescriptions reviewed in the audit were of poor quality with additions and crossings out [2]. Poor communication is also cited as a reason that errors occurred. The National Chemotherapy Advisory Group (NCAG) paper – *Chemotherapy services in England: ensuring quality and safety* [3], clearly recommends that prescription verification and dispensing (of chemotherapy) should only be undertaken by appropriately trained staff.

E-prescribing

The National Cancer Action Team, which is responsible for improving patient experience in the UK, issued the *Manual for Cancer Services – Chemotherapy Measures*. The measures state that all NHS providers of chemotherapy must use computer-generated prescriptions. ICHNT has this year successfully introduced a new e-prescribing system at the St Mary's site which previously used paper-based prescription pro formas. Although no formal assessment has been undertaken, it is believed that the introduction of the electronic system will reduce prescribing errors, e.g. omitted medication and incorrectly calculated

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doses. The computer-generated prescriptions also eliminate ambiguity associated with illegible handwriting or hand amendments on the prescriptions. There is an electronic trail of any amendments or interventions made and the facility to include notes and endorsements, often lacking on paper prescriptions.

E-prescribing allows easy access to previous prescriptions and provides information on any previous dose modifications and dates of administration to aid the verification process.

Both dose capping and maximum number of cycles of chemotherapy are programmed into the regimen to ensure there is no overdose and to ensure that chemotherapy is not continued beyond the recommended number of cycles.

However, e-prescribing may introduce other types of errors, e.g. incorrect programming of the regimen onto the system could lead to repeated errors. It is essential that healthcare staff are trained appropriately to avoid unintentional misuse of the system, e.g. amending chemotherapy volumes or incorrectly entering patient data.

ICHNT has procedures in place to reduce these risks and a training programme for all staff has been developed. All regimens are built by a chemotherapy-trained pharmacist, then validated by a cancer specialist pharmacist and finally checked and signed off by a consultant. Staff using the system are trained before being issued with a password to use the system and user manuals are easily accessible on the Trust's Intranet. All patient data are checked by both a nurse and a pharmacist.

Currently, ICHNT is introducing a new pathology results reporting system that will interface with the chemotherapy e-prescribing system to eliminate the risk of incorrect manual entry.

Error reporting and management

ICHNT uses the Datix electronic system for incident reporting. Within the cancer services at ICHNT the average incident reporting rate is around four in every 100 admissions for all incidents including medication, the national average is 5.5.

Individual errors are assigned an investigator who is responsible for ensuring all the facts relating to the incident are

obtained, e.g. exact nature of error, what measures have been taken/are required to immediately rectify the error, factors that contributed to the error, the outcome and likelihood of the incident recurring. This root-cause analysis is essential to establish that appropriate actions are taken to prevent recurrence.

Once a month, a summary of cancer medication errors is produced and discussed at the Trust's Cancer Clinical Incident Review Committee meeting, which is attended by the cancer pharmacist, the cancer clinical governance lead and senior nurses. Action points on serious errors are fed back to staff and measures implemented to prevent their recurrence. A more detailed quarterly report is also produced and discussed at the Cancer Quality and Safety meeting, where any recommendations are actioned.

Training and accreditation of staff

The NCAG report focussed on training and accreditation of all disciplines that are involved with the prescribing, dispensing and administration of chemotherapy. The British Oncology Pharmacy Association [4] introduced guidelines to assist pharmacists with screening chemotherapy prescriptions and ensures appropriate training of staff [5]. At ICHNT, all pharmacists undergo a training programme which consists of taught work, observing the senior pharmacists, a period of screening 'live' prescriptions which are then second-checked by the senior pharmacist and a log of these items. The trainees are exposed to a wide variety of different regimens and specialities. Once the senior pharmacist is satisfied, the trainee then undertakes a screening test under 'exam' conditions. Only if they have identified all errors can they be accredited to screen chemotherapy and put on the register.

Medical staff and non-medical prescribers must have undertaken local training before being accredited to prescribe chemotherapy. The content of this training includes knowledge of local treatment protocols and specific toxicities associated with the treatment [6]. ICHNT will soon be introducing

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a computer-based test that requires prescribers to demonstrate their competency. Only consultants, specialist registrars and experienced non-medical prescribers are allowed on to the chemotherapy prescribing register.

Nurses are usually the last check before a patient receives their chemotherapy and so it is essential that they are able to identify any errors that may have gone previously undetected. Nurses must hold an appropriate qualification in chemotherapy and have been assessed as competent to administer chemotherapy by a senior chemotherapy nurse. The content of the training includes the safe administration of chemotherapy and how to deal with the complications of chemotherapy. Accredited nurses are placed on the Trust's Chemotherapy Administration Register.

Intrathecal chemotherapy

In the UK in 2001, after an enquiry into the death of a teenager from the incorrect administration of vincristine, the Department of Health issued guidance on intrathecal chemotherapy (ITC) to ensure this mistake was never repeated. This guidance has since been updated twice, the last in 2008 [7]. The guidance sets strict standards on the procedures involved in the administration of ITC. Key points in the guidance are:

- there should be an Intrathecal Chemotherapy Lead for the Trust
- only trained and accredited staff on the intrathecal register may be involved in the process
- intrathecal chemotherapy must only take place in designated areas.

ICHNT has an Intrathecal Chemotherapy Committee that ensures compliance with the National Guidance. The committee is responsible for maintaining the local Intrathecal Policy and taking action whenever the UK National Guidance is updated, e.g. in 2008, the update included a recommendation that all adult vinca alkaloid doses should be administered in 50 mL mini-bags. There are designated trainers for nurses, doctors and pharmacy staff, to train and accredit staff prior to them being placed on the regis-

ter. The committee recently completed a risk assessment on its ITC service at the St Mary's site and decided that, as only a small number of ITC procedures were undertaken annually, i.e. fewer than 10, that it was safer not to administer ITC at St Mary's.

Enhancing capacity in cytotoxics preparation/compounding

Advanced prescribing

At ICHNT, we work closely with the prescribers to ensure that prescriptions are generated in a timely manner. The majority of patients can have 2–3 cycles prescribed in advance. There will always be the issue of patient delays and dose modification, but these are easier to accommodate if the majority of chemotherapy is made in advance. Advanced prescriptions can help to ensure that any interventions made by the pharmacists can be communicated to the prescriber and adjustments made to the prescription prior to the day of treatment. Hastily screened prescriptions can lead to prescribing errors not being identified, or not being rectified in time causing delays for patients.

Outsourcing

One approach to address capacity issues is to look at outsourcing some of the chemotherapy work to commercial manufacturers. Cytotoxics that

have relatively long expiries (28 days or more) and are high usage can be considered suitable for outsourcing where cost allows. In some cases, these drugs can be purchased at or around the same cost as vials; these then simply need to be dispensed for individual patients. This approach has been embraced across London and as a result, competitive pricing for a number of chemotherapy agents in ready-to-use forms has been achieved. One of the disadvantages is that nursing staff may have more than one syringe to administer and there has been at least one incident where a patient did not have all the syringes administered and as a result, received a lower dose than that planned.

Additionally, vial prices are rapidly changing, so all outsourced products need regular review to ensure outsourcing is not significantly increasing costs to the healthcare economy.

Vial sharing

At ICHNT we are developing a number of vial sharing schemes where doses of the same drug for a group of patients are made together on a campaign basis. This is more efficient, enables advanced preparation and produces cost savings. We prepare all trastuzumab doses in this way and have recently introduced



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this approach for borte-zomib. In both cases this is delivering significant cost savings to the healthcare economy as well as reducing patient delays. We are now considering the same approach for a variety of other drugs, where cost savings are less marked, as we believe the efficiency gains alone make this worthwhile.

Dose banding

ICHNT has been using dose banding and dose rounding for a number of years. Calculated doses are rounded to the nearest available dose size or combination of syringes within a 5% margin. The doses are then prepared or outsourced products are labelled prior to the patients' treatment date; these can be reissued to other patients if the patients' treatment is cancelled or the doses change. Not only does this lead to less wastage but it can reduce errors in dose calculation.

Automation in aseptics

In 2007, an automated compounding robot was installed in the aseptic unit at the Charing Cross site. We believed the robot would help to address some of the issues around safe handling, risk of repetitive strain in operators as well as delivering cost savings by vial sharing and increasing efficiency. Additionally, the robot uses a combination of barcode and camera technology to identify the products that are loaded. The robot weighs all products prepared to ensure that the correct dose of chemotherapy has been drawn up. We believe the risk of errors occurring during the compounding process is therefore significantly reduced compared to the manual process.

The robot has enabled us to review the skill mix within the aseptic unit moving towards having more lower-graded staff.

Capacity plans

It is a requirement of our licence that we have capacity plans in place in both aseptic units. Capacity planning is required

to ensure that adequate trained staff, equipment and facilities are available to meet workload pressures. The capacity plan aims to ensure that the:

- Quality of the product and safety of the operator are not compromised.
- Staff do not feel under extreme pressure.
- Staff do not overwork.
- Error rates do not increase.

To ensure that the aseptic unit can meet the demands being put upon it, a review of four areas is carried out annually:

- workload
- staffing
- facilities and equipment
- service quality.

A retrospective approach is taken with each area being compared against the previous year's data.

The plan addresses how to deal with short-term problems, e.g. staff sickness, planned shutdown of rooms/equipment; and long-term changes in staffing, facilities and workload. All staff within the aseptic units are aware of the plan and senior staff can invoke it as and when necessary.

Emergency chemotherapy/the need for a 24-hour compounding service

Although the Trust is a large oncology and haematology centre, the pharmacy aseptic units are only open Monday to Friday, 9 am to 5 pm, and there is no aseptic compounding service outside these hours. In order to ensure that patient needs can be met we have discussed this with consultants and identified a number of chemotherapy drugs which have been made available as standard doses for emergency use.

Future developments

It is planned that interfaces will be developed between the prescribing systems and the pharmacy systems to prevent double entry of data. This would significantly improve efficiency within our aseptic units.

The same technology that is used within the compounding robot to identify products and check that final doses are correct is being developed so that this will be available to use in clean rooms and isolators. This will prevent the need for a second member of staff to be available to carry out volume checks and should help to reduce errors during manual preparation.

Authors

Sarah Mahmoud, BPharm (Hons)
Senior Lead Cancer Pharmacist
Pharmacy Department

David Leonard, BPharm
Executive Lead Pharmacist
Aseptics and Clinical Trials

Professor Ann Jacklin, MPharmS, CHSM
Chief of Service
Pharmacy and Therapies

Imperial College Healthcare NHS Trust
Charing Cross Hospital
Fulham Palace Road
London W6 8RF, UK

References

1. National Patient Safety Agency. A themed review of patient safety incidents involving anticancer medicines 1 November 2003–30 June 2008; October 2010.
2. For better, for worse? National confidential enquiry into patient outcome and death. November 2008.
3. Chemotherapy services in England: ensuring quality and safety. A report from the National Chemotherapy Advisory Group. August 2009.
4. Standards for clinical pharmacy verification of prescriptions for cancer medicines. British Oncology Pharmacy Association. January 2010.
5. Guidance to support BOPA standards for clinical pharmacy verification of prescriptions for cancer medicines. British Oncology Pharmacy Association. March 2010.
6. Pan London guidelines for the safe prescribing, handling and administration of systemic anti cancer treatment drugs. April 2011.
7. Health service circular 2008/001: Updated national guidance on the safe administration of intrathecal chemotherapy. August 2008.

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Should monoclonal antibodies and their conjugates be considered occupational hazards

Thomas H Connor, PhD

Barbara A MacKenzie, BSc



Monoclonal antibodies are a novel class of agents that often lack information concerning hazards for healthcare workers. Their large molecular weights would be expected to limit bioavailability and toxic potential. However, actual bioavailability in occupational settings remains uncertain.

The toxicity of older-generation antineoplastic and other hazardous drugs has been well known since they were introduced in the 1940s. Because most of these antineoplastic drugs are non-selective in their mechanism of action, they affect non-cancerous as well as cancerous cells. In the 1970s, secondary malignancies were reported in patients who had previously received antineoplastic drugs for other malignancies [1]. Since that time, the International Agency for Research on Cancer has identified approximately 30 antineoplastic drugs as known or potential human carcinogens while many more are recognised as carcinogens based on laboratory research [2].

Although many safety provisions have been advanced to reduce exposure, recent studies have shown that workers continue to be exposed to these drugs despite safety policy improvements [3-5]. In 2004, the National Institute for Occupational Safety and Health (NIOSH) reviewed existing guidelines and published an alert reviewing the most recent information available and promoting a programme of safe handling during their use [1]. This alert included a listing of drugs that should be handled as hazardous. This list was updated in 2010 [6] and will be updated again in 2012 to keep abreast of new FDA drug approvals and warnings on existing drugs. The alert covers all workers in healthcare settings who are potentially exposed to hazardous drugs. Because of the expanding use of hazardous drugs into new areas and specialties, the number of workers who

are not properly trained in their safe handling will continue to increase.

Reports have associated workplace exposures to conventional antineoplastic drugs with acute health effects such as hair loss, headaches, acute irritation, and/or hypersensitivity. In addition, adverse reproductive outcomes—including infertility, spontaneous abortions, and congenital malformations—and evidence of teratogenic outcomes in patients and healthcare workers have been reported [1, 7]. During the past 30 years, professional organisations and government agencies around the world have developed guidelines to protect healthcare workers from adverse effects associated with occupational exposure to antineoplastic drugs [1].

NIOSH [1] adopted a set of six criteria to identify the characteristics of a hazardous drug, see Table 1. Since each drug is unique and varies considerably in structure, biological activity, bioavailability, formulation, and other characteristics, NIOSH evaluates each drug on an individual basis and not as a member of a specific class. For example, the American Hospital Formulary Service [8] currently lists monoclonal antibodies, including conjugated forms, as one of eight categories of antineoplastic drugs, see Table 2. Because they are proteins in nature, monoclonal antibodies themselves are not required to be evaluated for carcinogenicity or genotoxicity, even if their therapeutic effects are directly mediated by antibody binding to a target antigen. However, monoclonal antibodies may

be conjugated to other carcinogenic or genotoxic agents in order to target those toxic agents to specific cell types. For example, gemtuzumab ozogamicin was marketed in the US until 2010 [9]. The monoclonal antibody component of the drug targeted it to CD33, a cell surface antigen found on leukaemic blast cells. The toxic agent to which the anti-

Table 1: NIOSH criteria for hazardous drugs [1]

Carcinogenicity
Teratogenicity or developmental toxicity
Reproductive toxicity in humans
Organ toxicity at low doses in humans (> 10 mg/day) or animals (> 1 mg/kg/day)
Genotoxicity
New drugs that mimic existing hazardous drugs in structure or toxicity

NIOSH: National Institute for Occupational Safety and Health.

Table 2: American Hospital Formulary Service Classification 10:00 Antineoplastic Agents [8]

Alkylating agents
Antibiotics
Antimetabolites
Topoisomerase II inhibitors
Hormonal agents
Monoclonal antibodies
Interferons
Vaccines

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body was conjugated, a calicheamicin cytotoxic agent, worked by binding to DNA [10].

Although they may be applicable to bioactive agents conjugated to monoclonal antibodies, three of the six NIOSH criteria—carcinogenicity, genotoxicity, and new drugs that mimic existing hazardous drugs in structure or toxicity—are not applicable to the monoclonal antibodies themselves because of their unique characteristics. An additional three criteria might apply to either unconjugated or conjugated monoclonal antibodies:



teratogenicity or developmental toxicity, reproductive toxicity in humans, and organ toxicity at low doses in humans (> 10 mg/day) or animals (> 1 mg/kg/day). For many of the therapeutic monoclonal antibodies and conjugates, little information is available on these criteria. The majority of the monoclonal antibodies, according to the manufacturers' drug package inserts, fall in FDA Pregnancy Category C*.

Currently, only one monoclonal antibody has a safe handling warning recommended by the manufacturer. Brentuximab vedotin, a conjugated monoclonal

antibody that contains the microtubule disrupting agent *monomethyl auristatin E*, has safe handling guidelines and is also listed as Pregnancy Category D [11].

In the 1970s, a study from Finland indicated that healthcare workers may be at risk of harmful effects from antineoplastic drugs as a result of possible drug uptake from occupational exposure [12]. Since then, reports from several countries have documented drug contamination of the workplace, identified drugs in the urine of healthcare workers, and measured genotoxic

responses in workers [1, 3-5]. Exposure of healthcare providers to antineoplastic drugs is varied based on unique settings, but the routes of exposure are typically inhalation or dermal. Workers may be exposed by inhalation via droplets, particulates, and vapours when they create aerosols, generate dust by crushing tablets, and clean up spills and bodily wastes. Dermal exposure may occur when workers touch surfaces that are contaminated with hazardous drugs during their preparation, administration, or disposal. Exposure can also result from contact with surfaces contaminated with the waste products

of patients treated with these drugs that may contain the parent drugs and/or metabolites of the drugs. Additionally, oral exposure from hand-to-mouth contact and accidental injection with an antineoplastic drug, although rare, has been documented [1]. These studies have dealt with conventional lower molecular weight compounds and not with high molecular weight monoclonal antibodies and conjugates that target specific antigens on cell surfaces.

Dermal exposure to monoclonal antibodies

Given their large molecular weight (> 140 kDa) the potential for dermal uptake of unconjugated monoclonal antibodies or intact conjugates in the occupational setting is very low. Research has postulated the upper limit for dermal absorption of compounds at 500 Daltons [13]. However, local irritation or allergic reactions in damaged skin might facilitate dermal uptake [10]. Healthcare workers in general, and especially nursing personnel, have an unusually high incidence of dermatitis [14, 15], which could possibly contribute to dermal uptake of the monoclonal antibodies. Approximately one in three nurses has some form of dermatitis. Routine use of gloves when handling monoclonal antibodies is recommended and would prevent possible dermal uptake by normal or damaged skin.

Inhalation exposure to monoclonal antibodies

The bioavailability of high molecular weight substances (> 100 kDa) has been estimated at a maximum of 5% by inhalation. Given the much higher molecular weights of monoclonal antibodies, the absorption rate of unconjugated monoclonal antibodies or intact conjugates will probably be even lower [16]. If monoclonal antibodies were to be administered to patients by aerosolisation, the potential for exposure of the healthcare worker would be increased. The feasibility of delivery by aerosolisation of one unconjugated monoclonal antibody drug, cetuximab, has been explored and suggests a potential method of drug delivery [17]. However, since monoclonal

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antibodies are not usually administered by aerosolisation, their routine administration should not expose healthcare workers to conditions that could result in substantial exposure by inhalation.

Oral exposure to monoclonal antibodies

While it is possible that hand-to-mouth transmission of drugs can take place, any exposure to monoclonal antibodies by the oral route would result in denaturation and digestion in the gastrointestinal tract [10], severely limiting exposure to the monoclonal antibody itself by this route. However, this might, in theory, release lower molecular weight agents from conjugates which could then act directly on the gastrointestinal tract or be absorbed systemically.

In some cases, a monoclonal antibody may be conjugated with a radioactive moiety as in the case of ibritumomab tiuxetan and tositumomab. As radiopharmaceuticals, these monoclonal antibodies fall into a separate class of hazards that are under the control of nuclear regulatory agencies and require special handling due to their radioactivity.

Two approaches have been published that have attempted to characterise the occupational risk of handling monoclonal antibody-containing therapeutic agents. Langford et al. [18] developed a risk assessment tool based on the antigenic properties and the toxic potential of monoclonal antibodies and conjugates. These authors recommended that the majority of monoclonal antibodies available in the UK at that time should be considered high to moderate risk and should only be prepared in the pharmacy. A smaller group of monoclonal antibodies was considered low/moderate risk and could be prepared in the clinic if need be. However, given the complex nature of preparation for some monoclonal antibodies and the need for aseptic preparation conditions, preparation outside the pharmacy is not recommended [19].

Halsen and Krämer evaluated a number of monoclonal antibody-containing

agents based on reproductive and developmental toxicity and effects on fertility [10]. For the majority of these agents, the authors reported that significant data were lacking for these endpoints. However, they concluded that all of the monoclonal antibodies they evaluated had the potential for some level of reproductive toxicity. They also concluded that oral and dermal exposure to these agents would be very minimal. They postulated a possible exposure scenario by inhalation of aerosols but speculated that this route would also result in minimal exposure.

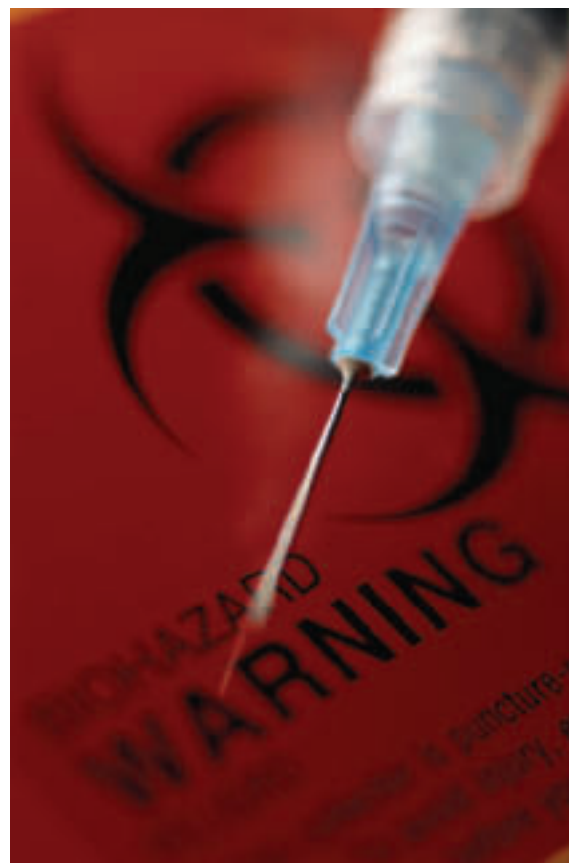
A recent publication describing a three-tiered approach to the safe handling of hazardous drugs [20] considered drug molecular weight as an important consideration in formulating recommendations to exclude all interferons and monoclonal antibodies from their three proposed risk categories: high-, low-, or reproductive-risk.

Given the uncertainties surrounding the handling of monoclonal antibodies, the following issues have been observed and will require careful consideration in classifying monoclonal antibodies as occupational hazards:

- In most cases, the amount of information available on the toxicity of monoclonal antibody-containing therapeutic agents, whether conjugated or unconjugated, is limited.
- Testing monoclonal antibodies for carcinogenicity or genotoxicity is typically not required by regulatory agencies and therefore these important criteria are not usually available.
- Though the potential for uptake of monoclonal antibodies by healthcare workers appears to be low (due to large molecular weight > 140 kDa), long-term, low-dose exposure to monoclonal antibodies may result in sensitisation of healthcare workers,

particularly if the monoclonal antibodies are xenogeneic. However, if small toxic agents were released from conjugates, they could potentially pose a greater problem.

- If healthcare workers become sensitised through occupational exposure it could limit treatment of those sensitised workers if they require treatment for cancer and other illnesses in the future.
- Dermatitis and other damage to the skin may facilitate the dermal uptake of monoclonal antibodies.



- The normal preparation and administration by healthcare workers of monoclonal antibodies should not result in the formation of aerosols sufficient to be an inhalation hazard. However, when the monoclonal antibodies are administered as aerosols, the potential for exposure of healthcare workers is increased.
- Many monoclonal antibodies are under development or are being approved, requiring continual attention.

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Overall, the potential for occupational exposure of healthcare workers to unconjugated monoclonal antibodies and intact conjugates is generally minimal. Exposure scenarios that apply to lower molecular weight antineoplastic drugs do not apply to intact protein-based molecules with the molecular weights of the monoclonal antibodies. Thus, potential for disassociation of conjugates may be an important consideration in the assessment of healthcare worker risk. The approach by NIOSH in evaluating drugs as potential occupational hazards is to evaluate each drug on an individual basis and not as a member of a group. Monoclonal antibodies that have been evaluated by NIOSH to date have not met the current criteria for a hazardous drug. However, if new information becomes available on a specific monoclonal antibody, NIOSH will review that information and re-evaluate the hazard potential. Thus, monoclonal antibodies currently in use or new approvals may be listed as hazardous drugs as more information becomes available.

Given the complex procedures for the preparation of some of the monoclonal antibodies and the requirement for aseptic preparation, many of the same procedures used in the preparation of the drugs identified as hazardous should apply to the preparation of monoclonal antibodies. Preparation should be performed in a biological safety cabinet or an aseptic compounding isolator using proper procedures and personal protective equipment. Following these procedures will protect both the integrity of the monoclonal antibody and the health of the worker [1, 19].

**Pregnancy Category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Available from: depts.washington.edu/druginfo/Formulary/Pregnancy.pdf*

Authors

Thomas H Connor, PhD
Research Biologist

Barbara A MacKenzie, BSc
Health Scientist

Division of Applied Research and
Technology
National Institute for Occupational
Safety and Health
Centers for Disease Control and
Prevention
4676 Columbia Parkway MS C-23
Cincinnati, OH 45226, USA

References

1. Connor TH, Burroughs GE, McDiarmid MA, Mead KR, Power LA, Reed LD. NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2004-165 (2004). Available from: www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf
2. IARC [2011] IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Lyons, France: World Health Organization, International Agency for Research on Cancer. [cited 2011 August]. Available from: monographs.iarc.fr
3. Connor TH, DeBord DG, Pretty JR, Oliver MS, Roth TS, Lees PS, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med.* 2010 Oct;52(10):1019-27.
4. Schierl R, Bohlandt A, Nowak D. Guidance values for surface monitoring of antineoplastic drugs in German pharmacies. *Ann Occup Hyg.* 2009 Oct;53(7):703-11.
5. Turci R, Minoia C, Sottani C, Coghi R, Severi P, Castriotta C, et al. Occupational exposure to antineoplastic drugs in seven Italian hospitals: the effect of quality assurance and adherence to guidelines. *J Oncol Pharm Pract.* on-line publication, 2010 Sept. Available from: opp.sagepub.com/content/early/2010/09/06/1078155210381931.full.pdf+html
6. MacKenzie BA, Connor TH, DeBord DG, Trout DB, O'Callaghan J. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2010. Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2010-167 (2010). Available from: www.cdc.gov/niosh/docs/2010-167/pdfs/2010-167.pdf
7. Lawson CC, Rocheleau CM, Whelan EA, Hibert EN, Grajewski B, Spiegelman D, et al. Occupational exposure to anesthetic gases, antineoplastic drugs, antiviral drugs, sterilizing agents, and X-rays and risk of spontaneous abortion among nurses. *Am J Epidemiol.* 2011;173(Suppl 11):S1-S316. doi: 10.1093/aje/kwr181
8. McEvoy G, Snow E, editors. American Hospital Formulary Service Drug Information. Bethesda, MD: American Society of Health-System Pharmacy; 2011.
9. FDA Press Release, June 21, 2010. Available from: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm216448.html
10. Halsen G, Krämer I. Assessing the risk to health care staff from long-term exposure to anticancer drugs—the case of monoclonal antibodies. *J Oncol Pharm Pract.* 2011 Mar;17(1):68-80.
11. Drug Package Insert: brentuximab vedotin. Seattle Genetics, Inc; [updated 2011 August]. Available from: www.adcetris.com/_pdf/Adcetris_USPI_2011.pdf
12. Falck K, Gröhn P, Sorsa M, Vainio H, Heinonen E, Holsti LR. Mutagenicity in urine of nurses handling cytostatic drugs. *Lancet.* 1979 Jun 9;1(8128):1250-1.
13. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol.* 2000 Jun;9(3):165-9.
14. Health and Safety Executive. Work-related contact dermatitis in the health services. Available from: www.hse.gov.uk/skin/employ/highrisk/healthcare.html
15. Kedrowski DA, Waeshaw EM. Hand dermatitis: a review of clinical features, diagnosis, and management. *Dermatol Nurs.* 2008 Feb;20(1):17-25.
16. Folkesson HG, Weström BR, Karlsson BW. Permeability of the respiratory tract to different-sized macromolecules after intratracheal instillation in young and adult rats. *Acta Physiol Scand.* 1990 Jun;139(2):347-54.
17. Maillot A, Congy-Jolivet N, Le Guellec S, Vecellio L, Hamard S, Courty Y, et al. Aerodynamic, immunological and pharmacological properties of the anticancer antibody cetuximab following nebulization. *Pharmaceut Res.* 2008 Jun;25(6):1318-26.
18. Langford S, Fradgley S, Evans M, Blanks C. Assessing the risk of handling monoclonal antibodies. *Hosp Pharm.* 2008;15:60-4.
19. US Pharmacopeial Convention [2011]. USP 34-NF 29. Pharmaceutical compounding sterile preparations. Chapter 797. 34th ed. Rockville, MD: United States Pharmacopeial Convention.
20. Chaffee BW, Armitstead JA, Benjamin BE, Cotugno MC, Forrey RA, Hintzen BL, et al. Guidelines for the safe handling of hazardous drugs: consensus recommendations. *Am J Health Syst Pharm.* 2010 Sept 15;67(18):1545-6.

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Obtaining insurance coverage for the use of closed systems in Japan



**Shin-ichi Sugiura, PhD; Mika Asano, BS; Hiroshi Gohma, PhD
Hirokazu Nakanishi, PhD; Tohru Hashida, PhD; Masahiro Okuda, PhD**

This article examines the current situation and possible answers to why healthcare professionals changed their mind on the importance of implementing closed systems, and steps taken to obtain coverage for the use of closed systems in the formulary services of the Japanese insurance system.

Introduction

Little attention has been paid to the hazards to which healthcare professionals may be exposed from the drugs administered to patients.

All drugs can produce adverse reactions in patients and also in healthcare professionals. It is known that certain specific drugs, even at very low concentrations, pose hazards to the workers handling them or working in the vicinity.

The American Society of Health-System Pharmacists addressed the problems of hazardous drugs in 1990. Their concerns have since been shared by the current Occupational Safety and Health Administration. If there is a risk that exposure to a drug may induce cancer, developmental or reproductive toxicity, or organ damage, the drug is classified as a hazardous drug. Many hazardous drugs are used for cancer chemotherapies and for the treatment of some infections. The therapeutic benefits of hazardous drugs outweigh the risk of adverse reactions to patients, however, exposed healthcare professionals are at risk of the same adverse reactions and for them, the risk-benefit relationship is not so positive. Exposure of healthcare professionals to hazardous drugs has been reported [1-3] to produce acute symptoms such as skin rash and chronic effects including reproductive adverse reactions and Skov et al. have also reported that it can cause cancer.

Some guidelines have been established concerning the handling of hazardous

drugs, but reports suggest problems in compliance with regard to the guidelines. Moreover, a small amount of hazardous drug has been detected in the urine of healthcare professionals who prepare or administer hazardous drugs even after applying safety protection, and environmental contamination by hazardous drugs has been reported in a survey of patient care surroundings even when handling guidelines have been followed.



Drugs. Despite such conditions, antineoplastic agents have been prepared on the ward in Japan, administered using inadequate safety protection, and disposed of without taking any appropriate measures. Closed transfer systems such as the PhaSeal system can reduce such prob-

lems but have not gained widespread use, primarily because of the high cost.

However, we have a fee structure to cover the use of a closed transfer system during the preparation of drugs for a patient.

In this article, we will examine the current situation and will attempt to answer the following questions: why did healthcare professionals change their minds regarding the importance of implementing closed systems, and how is it possible to obtain coverage for the use of closed systems in the formulary services of the Japanese insurance system?

In developing and industrialised countries alike, efforts to provide healthcare, including pharmaceutical care, are facing new challenges. Activities of the subcommittee of the Japanese Society of Hospital Pharmacists (JSHP) have also been challenged by problems of occupational exposure. The process used to resolve these issues is described below.

Process of the Japanese Society of Hospital Pharmacy work

JSHP established a third subcommittee to study pharmacy practice in 2003. The purpose of this committee was to devise JSHP guidelines on quality assurance for pharmacy-prepared sterile products. The members of this subcommittee are also members of the Japanese Society of Oncology Pharmacy Practitioners. The committee began to study the problem of

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occupational exposure for hazardous drugs by the following:

Creation of a network database system for the core hospital

Establishment of a national network with Ubiquitous Mobile Infrastructure (UMIS) for surveillance. The Knowledge Information Collaborating Network (KinCoNet) system enabled the partitioning of the server into areas of exclusive use for separated questionnaire counts. UMIS is a mobile infrastructure system which enables a mobile phone to serve as a data input terminal. Two systems were connected for the network database and analysed the results from 270 of 375 registered hospitals. The aim of this system was to understand the current views of hospital personnel with regard to the prevention of environmental exposure to hazardous drugs using a field survey method. Out of 270 core hospitals, 183 responded to the questionnaires within a week. Almost all hospitals (96.7%) identified that they needed closed transfer devices such as the closed system to restrict contamination. However, only 52 (28.4%) were able to implement these devices because of the costs associated with the devices. The majority (85.8%) needed to conduct a wipe study to clarify the extent of contamination by these drugs. This result was used to revise health insurance reimbursement policies for this activity by the JSHP.

The conduct of several studies into the exposure to hazardous drugs

1. A pilot study [4] of environmental and biological monitoring of occupational exposure to cyclophosphamide (CP) in two departments. The purpose of this pilot study was to verify if CP contamination was a significant problem in the Japanese hospital environment. We used a measure of CP to estimate the extent and seriousness of environmental contamination and exposure of staff caring for patients with haematopoietic cancer. At Nagoya University Hospital, Nagoya, Japan, in February 2006, two departments, A and B, were monitored with surface-wipe,

and urine samples were analysed using the Sessink method (exposure control, The Netherlands). Department A had a preparation room with biological safety cabinet (BSC) where the pharmacists prepared cytotoxic drugs. Department B did not have a BSC. Regardless of the use of BSC, wards were contaminated with CP. The contamination may be seen in routine handling because of the sealing used in CP containers and administration tubes when discarding them. CP was detected only once in the urine of a medical doctor who prepared CP by warming it.



2. A multicenter study [5] for environmental and biological monitoring of occupational exposure to CP in Japan. The purpose of this multicentric study was to clarify the current state of environmental contamination and exposure of healthcare professionals to hazardous drugs at six hospitals in Japan. Environmental contamination with CP, a hazardous drug considered to be carcinogenic (WHO criteria: class I), was investigated at six hospitals handling this drug. Wipe and urine examinations were performed at each facility. As a result of wipe examination, contamination with CP was identified at 50% of the

sites. The concentration was high (CP > 1.00 ng/cm²) in the general environment in two hospitals and in the safety cabinet in one hospital. In the survey for the exposure of staff to anticancer drugs, 276 samples were obtained from 41 healthcare professionals. CP was detected in 90 samples obtained from 23 subjects. The amount of exposure varied greatly between the facilities. The urinary excretion of CP per subject was between 2.7–462.8 ng/24 h. The range of urinary excretion for each hospital was between 4.6–211.2 ng/24 h.

3. An environmental and biological study of occupational exposure to CP in the pharmacy of a Japanese community hospital designated for the treatment of cancer [6].

The purpose of this study was to update the standard operating procedure (SOP) for hazardous drugs established by the JSHP and to understand if it was sufficient to prevent contamination by using a closed system. Applying the JSHP SOP, the hazardous drug, CP, was again detected in the urine of all four compounding pharmacists, though the mean CP level was reduced from 165.3 to 47.4 ng/24 h. after the revision of the SOP. Although there was no correlation between the amount of CP compounded and the CP levels in urine initially, the two values were significantly correlated after revision of the SOP ($R^2 = 0.87$).

Institution of a measurement system of CP on business

Wipe and urine studies were conducted under the supervision of JSHP subcommittee members. All samples were measured using a gas chromatography-tandem mass spectrometry (GC-MSMS) system and GC-MS method and were sent to Exposure Control BV in The Netherlands under refrigeration after collection. These studies require complicated and expensive procedures, so members of the subcommittee developed a public-private partnership to create a new measurement system of CP. The Kobelco Research Institute, Japan, orchestrated the joint develop-

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ment of a new method that used liquid chromatography (LC-MSMS). Using this system, Japanese International Society of Oncology Pharmacy Practitioners members reported on the results and then discussed the implications. The expense of using a measurement system was 80 Euros per seven samples for LC-MSMS.

A proposal to the Ministry of Health, Labour and Welfare

Two health insurance payment systems exist: fee for services and the Japanese Diagnosis Related Groups (DRG) diagnosis procedure combination. We cannot obtain reimbursement for preparations on the DRG system, although technical fees for preparation of sterile products can be billed under both. A hospital needs to satisfy certain objectives for facilities in order to obtain reimbursement. These conditions include having sufficient staffing and a qualified NASA (National Aeronautics and Space Administration) as class 100 cabinet. The fee allows a once-daily preparation for each patient. The fee for each inpatient is 500 yen/day and for each outpatient is 4,000 yen/day.

The JSHP activities related to the study and surveillance discussed above resulted in changes in policy under the health insurance system. The fee for preparations using a closed device is Japanese Yen 500/day. This additional fee has been in effect since 2010. It is epoch-making that such a fee was implemented to protect the safety of health professionals.

Conclusion

Over the past two decades, there has been a trend for pharmacy practice to move away from its original focus on supplying medicine toward a more inclusive focus on patient care. The role of the pharmacist has evolved from that of supplier of pharmaceutical products towards that of a provider of patient care. Nevertheless, there has been little attention to the role of pharmacist as it relates to occupational risk. The approval of fees by the Japanese health insurance system for the use of a closed device for drug preparation is the first such event in the world. We would like to encourage the use of similar systems in other parts of the international community.

Author for correspondence

Shin-ichi Sugiura, PhD (see photo)
Studies of Medical System Management
Nagoya University Graduate School of Medicine
65 Tsuruma-cho, Showa-ku
JP-466-8560 Nagoya, Japan

Co-authors

Mika Asano, BS
Studies of Letter, Kinjo University
Nagoya, Japan

Hiroshi Gohma, PhD
Studies of Medical System Management
Nagoya University Graduate School of Medicine, Nagoya, Japan

Hirokazu Nakanishi, PhD
Department of Clinical Pharmacy
Doshisha Women's College
of Liberal Arts, Nagoya, Japan

Tohru Hashida, PhD
Department of Pharmacy
Kobe City Medical Center
General Hospital, Kobe, Japan

Masahiro Okuda, PhD
Department of Clinical Pharmacy
and Biopharmaceutics
Mie University Graduate School
of Medicine, Mie, Japan

References

1. Valanis B, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med.* 1999;41(8):632-8.
2. Peelen S, Roeleveld N, Heederik D, Krombout H, de Kort W. Toxic effects on reproduction in hospital personnel. The Netherlands: Elsevier, 1999.
3. Skov T, Maarup B, Olsen J, Rorth M, Winthereik H, Lyng E. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. *Br J Ind Med.* 1992;49:855-61.
4. Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T. Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide. *J Oncol Pharm Pract.* 2011 Mar;17(1):14-9.
5. Sugiura S, Nakanishi H, Asano M, Hashida T, Tanimura M, Hama T, et al. Multicenter study for environmental and biological monitoring of occupational exposure to cyclophosphamide in Japan. *Oncol Pharm Pract.* 2011 Mar;17(1):208.
6. Tanimura M, Yamada K, Sugiura S, Mori K, Nagata H, Tadokoro K, et al. An environmental and biological study of occupational exposure to cyclophosphamide in the pharmacy of a Japanese community hospital designated for the treatment of cancer. *Journal of Health Science.* 2009;55(5):750-6.

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Common toxicities of oral anticancer agents: an overview



Phebe Si, BScPharm (Hons) Assistant Professor Alexandre Chan, PharmD

Oral anticancer agents have many benefits for patients, but side effects can still arise. In this article, we review and evaluate the current recommendations for the management of some of the most commonly observed toxicities among patients using oral anticancer agents.

Introduction

Over the past few years, there has been an observed paradigm shift in cancer treatment from parenteral to oral anticancer drug administration, see Table 1. This is evidently true as many of the newly approved anticancer agents, such as tyrosine kinase inhibitors (TKI), vascular endothelial growth factor (VEGF) inhibitor, mammalian target of rapamycin (mTOR) and epidermal growth factor receptor (EGFR) inhibitors are administered orally. Oral anticancer treatment offers patients great convenience and flexibility for the timing and location of drug administration, reduced use of healthcare resources, and, most importantly, a better quality of life as compared to parenteral anticancer therapy. Despite these benefits, regular monitoring with appointments and blood tests are still required with oral anticancer agents (OAs), as they are able to cause adverse side effects which are not any less severe than parenteral agents. Furthermore, responsibilities including the burden of self-administration, adverse effect monitoring and reporting are now shifted to the patients, and issues such as non-compliance may potentially compromise treatment effectiveness [1].

In this article, we review and evaluate the current recommendations for the management of some of the most commonly observed toxicities among patients using OAs.

Myelosuppression

Myelosuppression is inarguably the most disturbing toxicity of OAs. A number

of cytotoxics, such as cyclophosphamide, melphalan, procarbazine, capecitabine, hydroxyurea, methotrexate, capecitabine, temozolamide, vinorelbine, and targeted therapies including sunitinib, sorafenib, imatinib and everolimus may cause myelosuppression, including anaemia, thrombocytopenia and neutropenia among patients. Bone marrow suppression is generally dose-dependent and may occur within one week of treatment initiation [2]. Delayed myelosuppression, however, has been observed with certain agents such as lomustine [3].

Anaemia in cancer patients is usually multi-factorial. OAs can cause anaemia through directly impairing haematopoiesis in the bone marrow or indirectly through decreased erythropoietin production by the kidney. Effects accumulate over repeated cycles of therapy. Anaemia may cause considerable fatigue but can be managed by iron support, use of erythropoietin stimulating agents or packed red blood cell transfusions depending on the individual's symptoms and risk factors [4].

Clinical manifestations of chemotherapy-induced thrombocytopenia include petechiae, bruising, ecchymoses, epistaxis, bleeding from mucous membranes and severe purpura. Thrombocytopenia increases risk of bleeding which can potentially be fatal. However, spontaneous bleeding rarely occurs unless platelet counts drop below 20,000 cells/ μ L. Management is usually supportive but platelet transfusions may be considered for prevention or treatment of bleeding episodes [2].

Table 1: Oral anticancer agents

Traditional cytotoxic agents		
Altretamine	Fludarabine	Temozolamide
Busulfan	Hydroxyurea	Thioguanine
Capecitabine	Lomustine	Topotecan
Chlorambucil	Melphalan	TS-1
Cyclophosphamide	Mercaptopurine	UFT
Estramustine	Methotrexate	Vinorelbine
Etoposide	Procarbazine	
Targeted therapies		
Dasatinib	Lapatinib	Sunitinib
Erlotinib	Lenalidomide	Pazopanib
Everolimus	Nilotinib	Thalidomide
Gefitinib	Sorafenib	
Imatinib	Sirolimus	
Hormonal agents		
Aminoglutethimide	Flutamide	Raloxifene
Anastrozole	Letrozole	Tamoxifen
Bicalutamide	Medroxyprogesterone	Toremifene
Diethylstilbestrol	Megestrol	
Exemestane		
Others		
Azathioprine	Isotretinoin	Vorinostat
Bexarotene	Tretinoin	

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Neutropaenia may result in the suppression of the immune system and impairs the patients' ability to fight infections. Concomitant corticosteroids may also further weaken the immune system. Thus, close monitoring of these patients is necessary. Febrile neutropaenia is an oncologic emergency and immediate recognition and treatment is vital. Patients should be advised to maintain good hygiene by frequent hand washing, avoidance of uncooked foods, contact with fresh flowers/live plants, sick people or crowded areas wherever possible. Proper advice to seek prompt medical attention if signs and symptoms of infection such as fever, sore throat and ulcers are present should be emphasised such that timely intervention can be administered if needed. Use of granulocyte colony stimulating factors may reduce the duration and severity of neutropaenia and can be used prophylactically or as rescue therapy [2]. Prophylactic therapy may sometimes be necessary to defray the risk of opportunistic infections, such as *pneumocystis carinii* pneumonia (PCP), *candidiasis*, *aspergillosis* and reactivation of tuberculosis or hepatitis because the patient's immune system can be suppressed to a critically low level. PCP prophylaxis is mandated for all patients throughout the concomitant administration of temozolamide and radiotherapy during the 42-day regimen for newly diagnosed high grade glioma [5]. In addition, abstention from live vaccine usage during chemotherapy may also be required.

Oral mucositis

Cells in the oral cavity are subjected daily to external forces and inherently have a very high turnover. OAAs may affect these cells, resulting in mucositis. Certain OAAs, such as methotrexate and etoposide, are known to be excreted in the saliva and cause mucositis among cancer patients [6]. mTOR inhibitor associated stomatitis has also been coined to describe oral aphthous-like ulcer development that is associated with sirolimus and everolimus usage [7]. Although typically self-limiting, mucositis must be

properly managed as infectious complications may arise. Pain resulting from oral mucositis can also lead to a decreased oral intake, potentially leading to poor nutrition and dehydration. Treatment goals include the reduction of severity and duration of symptoms, relief of discomfort and prevention of infection until recovery. Prevention of mucositis through the maintenance of good oral hygiene is essential and options such as oral debridement and decontamination, lubrication with various available preparations and topical and systemic pain relief form an integral part of treatment management [8]. Patients should also be advised to avoid foods that may irritate the damaged mucosal lining such as hot, spicy, coarse or rough textured foods and foods containing citric acid/juices, alcohol or tobacco [6].



Diarrhoea

Diarrhoea is the dose-limiting and major toxicity of regimens containing fluoropyrimidines [9]. Capecitabine, the oral pro-drug of 5FU is commonly used in metastatic breast and colorectal cancers and has a high incidence of diarrhoea. The incidence of diarrhoea

with targeted agents is also rather high, ranging from 19% with everolimus use to 79% with imatinib use [10]. However, diarrhoea caused by OAAs is usually self-limiting over the first few days of treatment, and seldom warrants hospitalisation. Patients should be advised to prevent dehydration by adequate clear fluid intake and to avoid dietary triggers such as spicy foods, alcohol, caffeinated drinks such as tea and coffee, milk and dairy products or high fibre foods. Anti-diarrhoeal medication such as loperamide 4 mg at first bowel movement followed by 2 mg after each loose stool, up to a maximum of 16 mg/day and lomotil (diphenoxylate 2.5 mg, atropine 0.025 mg) two tablets up to four times a day may be prescribed if necessary [11].

Nausea and vomiting

Nausea and vomiting is another gastrointestinal side effect that is commonly associated with OAAs. Management is especially important for OAAs as inadequate control can affect delivery of accurate dose and lead to decreased treatment adherence affecting treatment outcomes and the patients' quality of life. Management is similar to that of parenteral anticancer agents. Common non-pharmacologic interventions include diet changes such as starting with bland foods, eating small but frequent meals and avoidance of foods which may serve as triggers such as caffeine, alcohol, spicy, greasy or foods with strong odors. The National Comprehensive Cancer Network 2011 guidelines on antiemesis recommends antiemetic prophylaxis for moderate to high emetic risk OAAs (such as temozolamide, procarbazine high dose cyclophosphamide (≥ 100 mg/m²/day), busulfan (≥ 4 mg/day), etoposide, single day lomustine, estramustine and altretamine) with oral 5-HT₃ antagonists (dolasetron/granisetrone/ondansetron) before chemotherapy initiation and then on an as needed basis. Prevention of nausea and vomiting for low/minimal emetic risk OAAs (for most targeted agents) can be achieved through the use of metoclopramide, prochlorperazine or haloperidol before chemotherapy and then on an as needed basis [12].

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Dermatological toxicities

A number of dermatological toxicities, such as rashes, pruritis, paronychia and xerosis, are commonly observed with newly approved targeted therapies, such as the epidermal growth factor receptor (EGFR) inhibitors. The EGFR is a transmembrane glycoprotein commonly expressed on many normal cells of epidermal origin such as the epidermis, sebaceous glands and hair follicular epithelium. It serves to maintain normal skin health, cell growth and proliferation. Thus, due to their mechanism of action, EGFR inhibitors such as gefitinib and erlotinib are associated with such dermatological toxicities and sometimes dose-limiting dermatologic/cutaneous toxicity. This distinctive toxicity occurs in approximately two-thirds of patients treated with EGFR inhibitors, with about 10% requiring dose interruptions or reductions. However, the presence of EGFR inhibitor rash is not a contraindication to use and seldom warrants treatment discontinuation. EGFR inhibitor rash has also been postulated to be related to clinical antitumor activity and may possibly be used prognostically to gauge patient's response to chemotherapy [13].

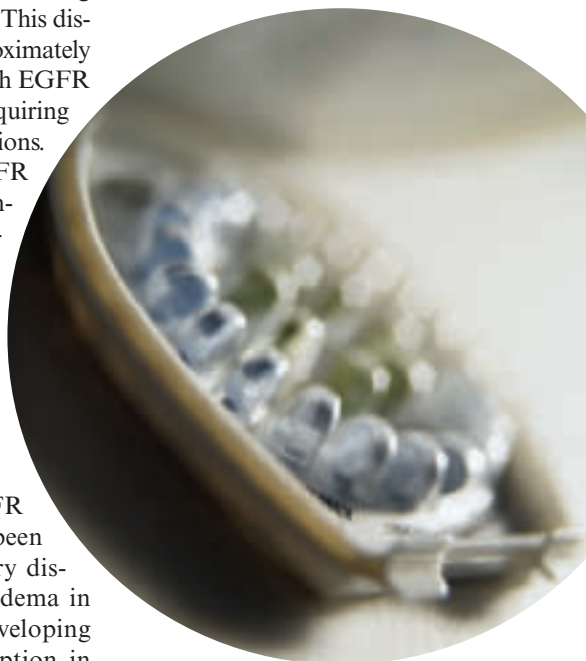
The clinical course of EGFR inhibitor mediated rash has been well characterised, with sensory disturbances of erythema and oedema in the first treatment week, developing further to papulopustular eruption in weeks one to three, leading up to crusting in week four [14]. Rash prevention strategies may improve over time and can generally be managed effectively with the use of topical agents such as emollients, steroids, moisturisers, antibiotic creams/gels and seldom require escalation to use of oral antibiotics such as doxycycline/tetracycline. However, erythema and dry skin may persist for up to six weeks [15].

Hand-foot syndrome, or palmar-plantar erythrodysesthesia (PPE) is a serious dose-limiting toxicity with capecitabine use. Severe reactions may warrant treatment interruptions, dose reductions or

even discontinuation. Targeted agents such as sunitinib and sorafenib are also known to cause PPE. Therapies such as the use of pyridoxine or vitamin B6, nicotine patch, vitamin E, topical emollients/creams and corticosteroids have been reported in the literature. However, well designed clinical trials are currently lacking [16].

Hot flushes

A prevalent and frequently bothersome side effect with these hormonal agents that may even require treatment alteration or cessation in patients is hot flushes. These are recurring, transient episodes of flushing and sweating, with a sensa-



tion of heat, oftentimes accompanied by palpitation or anxiety, and sometimes followed by chills, similar to menopausal symptoms. The pathophysiology has not been fully elucidated, but is thought to be due to a central nervous system anti-oestrogenic effect causing thermoregulatory dysfunction [17].

Management options include the use of antidepressants, lifestyle interventions to keep core body temperature low by dressing in layers, use of cotton clothing/beddings, drinking cold water, staying in an air-conditioned room, taking cold shower and identifying and avoiding triggers such as spicy food, smoking,

alcohol, and caffeine. Venlafaxine and paroxetine have been widely studied, and were shown to reduce hot flushes by more than 50%. Doses should be titrated up or downward very slowly and effects from antidepressant therapy are usually seen in two weeks, if not, switching to another agent can be considered. However, it is important to note that the concurrent use of potent CYP2D6 inhibitors such as paroxetine and fluoxetine may reduce the formation of highly anti-oestrogenic active tamoxifen metabolites 4-hydroxy-tamoxifen and 4-hydroxy-N-desmethyl-tamoxifen (endoxifen) and thus blunt the clinical effectiveness of tamoxifen, potentially resulting in decreased disease/progression-free survival, increased recurrences, and non response to therapy. Clinicians should avoid using agents that may potentially interact with antidepressants [17].

Bone disease

Bone disease is also a major concern with some OAs. Osteoporosis and bone loss increases risk of fractures and skeletal-related events and thus mortality and morbidity. Aromatase inhibitors (anastrozole, letrozole and exemestane) induced bone loss is a well established phenomenon and may be exacerbated by other breast cancer treatments such as ovarian ablation chemotherapy, steroid use, surgical oophorectomy and gonadotropin-releasing hormone agonists. However, this may be reversible upon treatment cessation. Risk factor evaluation before treatment initiation is therefore recommended. Lifestyle changes such as dietary modification, regular exercise, fall prevention, avoidance of excessive alcohol intake, smoking cessation, and adequate calcium and vitamin D supplementation should be considered as appropriate in all patients [18]. Bisphosphonate therapy is a mainstay of therapy for osteoporotic patients, but adverse effects may include hypocalcaemia and osteonecrosis of the jaw.

Venous thromboembolic events

Another significant side effect with some of these hormonal agents is the risk of

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venous thromboembolic events (VTEs) such as deep vein thrombosis and pulmonary embolism. Tamoxifen is associated with a significantly increased risk of VTE [19]. With high dose diethylstilbestrol use, some clinicians may even choose to prescribe concurrent prophylactic aspirin therapy as it is associated with high cardiovascular toxicity and mortality. Multiple myeloma regimens combining lenalidomide/thalidomide with dexamethasone have also been reported to be associated with a significant increase in the incidence of VTE. Clinicians should be aware of the significant additional procoagulant effects of these agents, especially when used in conjunction with parenteral chemotherapy. Patients should be informed about these risks and instructed to seek immediate medical attention if any of these symptoms present themselves.

Secondary malignancies

Drugs used to treat cancer are usually cytotoxic, teratogenic, and may also have the ability to cause secondary cancer (carcinogenic) through genotoxicity or other means. Even the non-cytotoxic hormonal agent tamoxifen has been shown in studies to increase the risk of endometrial cancer [19]. As such, safe handling of even oral cytotoxics through the use of the 'no touch' handling technique and emphasis on swallowing tablets whole, prohibiting any crushing and chewing to prevent aerosolisation is essential to protect patients, their caregivers, and the environment [20].

Conclusion

OAs are used globally in clinical practice for the management of various malignancies. However, they may also cause a variety of serious toxicities and adverse effects, which require supportive care management from healthcare

professionals. Healthcare professionals should be vigilant and monitor patients closely when they are using OAs.

Authors

Phebe Si, BScPharm (Hons)

Pharmacist

Department of Pharmacy

National Cancer Centre Singapore

11 Hospital Drive

SG-169610 Singapore

Assistant Professor Alexandre Chan

PharmD, MPH, BCPS, BCOP

Associate Consultant Clinical Pharmacist

Department of Pharmacy

National University of Singapore

18 Science Drive, Blk S4

SG-117543 Singapore

References

- McLeod HL, Evans WE. Oral cancer chemotherapy: the promise and the pitfalls. *Clin Cancer Res*. 1999 Oct;5(10):2669-71.
- Iannucci A, Chan, A. Management and treatment of hematologic toxicities. In: Ignoffo RJ, Viele CS, Ngo Z, editors. *Mosby's oncology drug reference*. 9th ed. Missouri: Mosby, Elsevier; 2007. p. 333-53.
- Lomustine [product insert]. Bristol-Myers Squibb. USA.
- National Comprehensive Cancer Network. *Cancer and Chemotherapy Induced Anemia*. V2.2012.
- Temozolamide [product insert]. Schering Corporation. USA.
- Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis-complicating the treatment of cancer. *Neoplasia*. 2004 Sep-Oct; 6(5):423-31.
- Campistol JM, de Fijter JW, Flechner SM, Langone A, Morelon E, Stockfleth E. mTOR inhibitor-associated dermatologic and mucosal problems. *Clin Transplant*. 2010 Mar-Apr;24(2):149-56.
- Treister NS. Chemotherapy-induced oral mucositis treatment & management. *Medscape reference*. [cited 2011 August 1]. Available from: emedicine.medscape.com/article/1079570-treatment
- Rustum YM, editor. *Fluoropyrimidines in cancer therapy*. New York: Springer-Verlag, Humana Press; 2003.
- Lexi-Comp, Inc. *Lexi-Drugs Online* [Internet]. 1978-2010. Available from: online.lexi.com/crlsql/servlet/crlonline
- Benson AB, Ajani JA, Catalano RB, Engeling C, Kornblau SM, Martenson JA Jr. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *Clin Oncol*. 2004 Jul;22(14):2918.
- National Comprehensive Cancer Network. *Antiemesis*. V1.2012.
- Giovannini M, Gregore V, Belli C, Roca E, Lazzari C, Viganò MG. Clinical significance of skin toxicity due to EGFR-targeted therapies. *J Oncol*. 2009;849051:1-8.
- Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. *Curr Oncol*. 2009 Jan;16(1):16-26.
- Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, Epstein JB, et al. MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011 Aug;19(8):1079-95. [Epub 2011 Jun 1].
- Gressett SM, Stanford BL, Hardwicke F. Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract*. 2006 Sep;12(3):131-41.
- Kligman L, Younus J. Management of hot flashes in women with breast cancer. *Curr Oncol*. 2010 Feb;17(1):81-6.
- National Osteoporosis Foundation. *Clinician's guide to prevention and treatment of osteoporosis 2010*. [Cited 2011 July 31]. Available from: www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v7.pdf
- Iqbal J, Ginsburg OM, Wijeratne TD, Howell A, Evans G, Sestak I, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. *Cancer Treat Rev*. 2011 Jul 18. [Epub ahead of print].
- Goodin S, Griffith N, Chen B, Chuk K, Daouphars M, Doreau C. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. *J Oncol Pract*. 2011 Jan;7(1):7-12.

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Safe dispensing of oral chemotherapy

Robert McLauchlan, BScPharm (Hons)



Oral chemotherapy presents a new challenge for hospital pharmacists in terms of patient safety and optimising patient care. It should be subject to the same rigorous checks as parenteral therapy. This article describes specific safety measures implemented at a major Australian teaching hospital.

Background

While some forms of oral chemotherapy have been available for decades, there has been rapid growth in the use of oral anticancer agents in recent years. This increase in the use of the oral route has occurred more quickly than many healthcare providers have been able to implement a stringent system of checking and monitoring such as exists for parenteral therapy. In most institutions each dose of parenteral chemotherapy is reviewed by more than one health professional prior to administration, body surface area and dose calculations are routinely checked by pharmacists; and written protocols and regimens are available. However, these safeguards are not yet widely in place for oral chemotherapy.

One of the primary drivers for the increase in the popularity of oral chemotherapy is patient preference, and it has been estimated that 90% of patients would choose oral treatment over IV chemotherapy [1]. However, not all patients are suitable candidates for oral chemotherapy and there must be a careful selection process in place. Many patients are under the mistaken impression that oral chemotherapy is somehow less toxic and safer than IV treatment, and pharmacists are in a position to help correct this misconception. The use of oral chemotherapy shifts much of the responsibility from oncology healthcare professionals back to patients and caregivers, and should be offered only to highly motivated patients capable of understanding and following the sometimes complicated, cyclical regimens involved [2, 3]. Patients need to be educated in the management of expected side effects and must understand very clearly

when they should seek medical advice. The decision to proceed with oral therapy requires multidisciplinary involvement of the healthcare team and ongoing support over the duration of therapy.

Hospital pharmacists have a vital role to play in managing the provision of oral chemotherapy by ensuring all the required checking procedures are in



place and that patients are fully educated about the chemotherapy regimen they are receiving.

Medication errors

There are numerous reports in the literature of prescribing, dispensing and administration errors involving oral chemotherapy, many of which have resulted in very serious outcomes [4-6]. A number of factors contribute to the likelihood of errors occurring with oral chemotherapy.

These include:

- misconceptions about oral chemotherapy
- complex, intermittent regimens
- confusing abbreviations and acronyms
- less direct supervision than parenteral chemotherapy
- lack of a comprehensive checking routine
- limited information available to pharmacy
- large variation in dosage making error detection difficult
- non-specialist pharmacists dispensing oral chemotherapy
- supply of excessive quantities
- inadequate patient education
- lack of multidisciplinary care.

Published recommendations

A number of organisations have published guidance on the use of oral chemotherapy [7-10]. Some common themes of these recommendations include pharmacists having access to relevant clinical information and treatment plans, the provision of information and education to patients, and limiting the quantities

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of oral chemotherapy supplied at any one time. Based on this published data, we set out in our pharmacy department at Austin Health to develop a policy and procedure on the provision of oral chemotherapy.

Supply of oral chemotherapy at Austin Health

The supply of oral chemotherapy at Austin Health occurs from the general outpatient dispensary and is largely handled by non-specialist pharmacists. Our department pharmacists (55 in total) were surveyed about their attitudes towards dispensing oral chemotherapy. When asked to rate their confidence on a numerical analogue scale from 0 to 10, 64% gave themselves a score of 5 or less (indicating they were not confident) despite 54% of respondents having dispensed some oral chemotherapy in the preceding month. When asked about educational resources and requirements, 100% of those surveyed stated that it was important for the department to develop resources and provide some form of education on oral chemotherapy and 82% stated that they would be interested in participating in any credentialling programme offered. The aspects respondents rated most important in an education programme were information on the chemotherapy regimens, side effect management, interpretation of laboratory results pertaining to chemotherapy, and effective counselling skills.

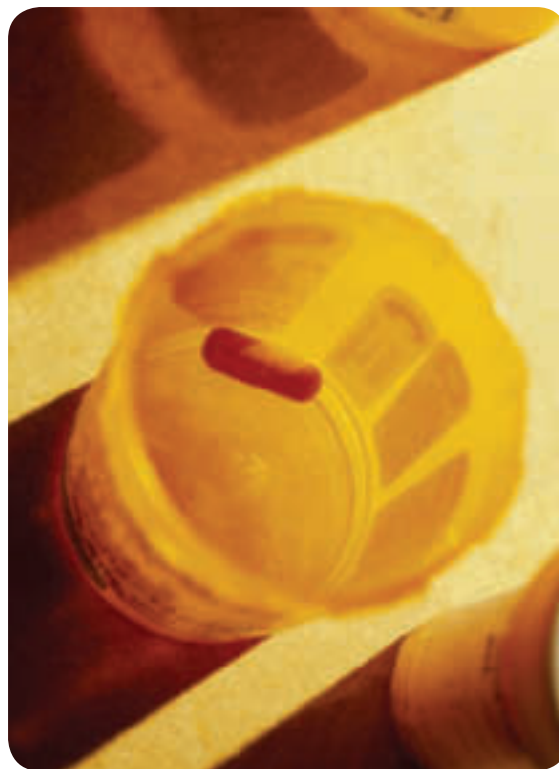
Development of departmental policy on oral chemotherapy

A small group, including two experienced oncology pharmacists, was established to develop a policy for the department. The first step in the process was to decide which drugs would be included. A risk stratification and scoring system was developed based on a number of criteria. The higher the score, the higher the assumed risk. For example, agents score more highly if treatment is cyclical; if combination therapy is used; if the drug is being used for non-marketed indica-

tions; if there are unique toxicities to be managed; and if specific supportive care agents need to be co-prescribed. A total of 17 drugs were included in our policy including cytotoxics, immunomodulators and tyrosine kinase inhibitors. In line with published standards, the policy applies only when these agents are supplied to cancer patients [9].

Key features of the policy

The key features of the oral chemotherapy policy include:



1. Pharmacist only handling

Only pharmacists are involved in the handling of oral chemotherapy prescriptions. Pharmacy technicians, pharmacy interns and students are not permitted to deal with any aspect of these prescriptions. This includes receiving the prescription, dispensing, checking, counselling and any interaction with prescribers and patients.

2. Mandatory check of relevant patient laboratory parameters

Prior to the supply of a cycle of oral chemotherapy, the dispensing pharma-

cist must check that all relevant laboratory results are appropriate. This includes review of the full blood examination and indicators of renal and hepatic function.

3. Supply of enough medication for one treatment cycle only

A number of the reported cases of medication misadventure with oral chemotherapy have occurred because patients have been given excess quantities of medication. Often the government funded/reimbursed quantity is far more than is required by the patient until their next review. For cyclical therapy, patients are provided with just the precise number of tablets or capsules to complete one course of therapy. For continuous therapy, enough medication may be provided to last until the patients next scheduled clinic visit if appropriate.

4. Inclusion of cycle start and stop dates, and rest period on dispensing label

For cyclical therapies, the date that the cycle is due to begin and end needs to be printed on the label of the dispensed medicine, together with any regimen specific rest period which follows the active treatment.

5. Documented provision of verbal and written patient information

Patients must be adequately educated about their therapy, and this includes the provision of both verbal and written information. The dispensing pharmacist must record that this education has been completed, must document what written information has been provided, and must record who the information was provided to (patient and/or carer) and also that a check of the patient's understanding has been carried out.

6. Check by a second independent pharmacist

Once dispensing is complete, a second pharmacist checks the accuracy of the dispensing, and checks that all of the mandated requirements have been met.

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7. Completion of checklist for each dispensing episode

For each dispensing a checklist is followed and completed and signed by both the dispensing and the checking pharmacist. The purpose of the checklist is to ensure that all the appropriate steps have been taken in the dispensing process, and forces all pharmacists to follow procedures employed by an experienced oncology pharmacist. Once completed, the checklist is image scanned together with a copy of the prescription form, making it extremely easy to retrieve if required.

Pharmacist printed resources

In conjunction with the oral chemotherapy policy and checklist, some resources have been developed for use by staff pharmacists. For frequently used regimens, this includes both a regimen resource and practice points for the dispensing pharmacist. The regimen pages include information on the indication, drugs, doses, rest periods and cycle frequency. The practice points contain valuable information for pharmacists including significant drug interactions, dose modification recommendations, anticipated toxicities, supportive care medications to be co-prescribed, and the counselling to be covered with the patient.

Education and training

Staff who regularly work in the pharmacy dispensaries were educated about the policy and the completion of the checklist. An experienced oncology pharmacist explained the requirements, and trained staff in the basic interpretation of laboratory tests, supportive care issues, and the management of side effects.

Outcomes

The implementation of this policy at our institution has been well accepted by pharmacy staff. An audit conducted three months after the introduction of these procedures indicated a 95% compliance rate with the completion of the oral chemotherapy checklist. Computer dispensing records revealed that start and stop dates and rest periods were included on more than 80% of dispensing labels. Initially there were concerns over patient waiting times, with an expectation that patients would have to wait significantly longer for the pharmacy to prepare their medications. An audit conducted three months before and three months after the implementation of the new policy showed that at one hospital, campus (A) waiting times had increased from an average of 27 minutes to 42 minutes, an increase of 15 minutes. At our second campus (B) there was no difference in waiting times before and after adherence to the oral chemotherapy policy. One reason for the difference in the waiting times at the two campuses may be the availability of an experienced oncology trained pharmacist who works regularly in the general dispensary at one hospital.

Conclusion

An oral chemotherapy policy and procedure has been successfully implemented at Austin Health and compliance with the requirements contained in the document is extremely high. The 15-minute increase in waiting time at campus (A) is considered acceptable in view of the potential reduction in medication errors and enhanced patient safety. Further work in this area needs to address if the implementation of this practice guide-

line has reduced the error rate and the incidence of medication misadventure.

Author

Robert McLauchlan, BScPharm (Hons)
Dispensary Manager
Austin Health
145-163 Studley Road
Heidelberg, Melbourne, Victoria 3084
Australia

References

1. Liu G, Franssen E, Fitch MI, et al. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol.* 2007;15:110-5.
2. Partridge AH, Avorn J, Wong PS, et al. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst.* 2002 May 1;94(9):652-61.
3. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-97.
4. Weingart SN, Toro J, Spencer J, et al. Medication errors involving oral chemotherapy. *Cancer.* 2010;116:2455-64.
5. Taylor JA, Winter L, Geyer LJ, et al. Oral outpatient chemotherapy medication errors in children with acute lymphoblastic leukaemia. *Cancer.* 2006;107(6):1400-6.
6. Moore TJ, Walsh CS and Cohen MR. Reported medication errors associated with methotrexate. *Am J Health Syst Pharm.* 2004;61:1380-400.
7. Weingart SN, Brown E, Bach PB, et al. NCCN Task Force Report: oral chemotherapy. *J Natl Compr Canc Netw.* 2008 Mar; 6 (Suppl 3):S1-14.
8. NHS National Patient Safety Agency. Oral anti-cancer medicines: risks of incorrect dosing. Available from: www.nrls.npsa.nhs.uk/resources/?entryId45=59880
9. SHPA Standards of practice for the provision of oral chemotherapy for the treatment of cancer. SHPA Committee of Specialty Practice in Cancer Services. *J Pharm Pract Res.* 2007;37(2):147-50.
10. Department of Health, Victoria, Australia. Quality use of medicines program. Caution with oral cancer treatments. Available from: www.health.vic.gov.au/qum/initiatives/hrm.html

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Speakers at the Fourth International Oncology Meeting, Salzburg, Austria



Paul JM Sessink, PhD
 President, Exposure Control BV
 Wijchen, The Netherlands

Shin-ichi Sugiura, PhD
 Director, JSOPP Japan
 Nagoya University Graduate
 School of Medicine
 Nagoya, Japan



Rachel E White, MA (Psych)
 University Health Network
 Toronto, Canada

Robert McLauchlan, BSc (Pharm)
 ISOPP Standards Chair
 Advisory Panel for MSSA
 St Vincent's Hospital
 Melbourne, Australia



Alexandre Chan, PharmD
 ISOPP Education Chair
 Faculty of Science
 National University of Singapore
 Singapore

Thomas H Connor, PhD
 National Institute for Occupational
 Safety and Health
 Cincinnati, Ohio, USA



Philip E Johnson
 Pharmacy Advocacy Director,
 FASHP
 Moffitt Cancer Center
 Tampa, Florida, USA

Carole Chambers, BSc (Pharm)
 ISOPP Past President
 Tom Baker Cancer Clinic
 Calgary, Canada



David Leonard, BPharm
 Imperial College Healthcare
 NHS Trust
 London, UK

Johan Vandembroucke, PharmD
 ISOPP President
 Advisory Panel for MSSA
 Universitair Ziekenhuis Gent
 Gent, Belgium

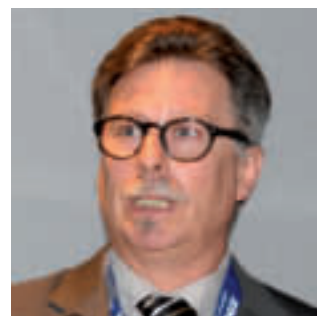


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From left, second row:

Roland Starlinger (International Product Manager, BU Oncology Injectables), Alexandre Chan (ISOPP Education Chair, Faculty of Science National University of Singapore, Singapore), Johan Vandembroucke (ISOPP President, Advisory Panel for MSSA, Universitair Ziekenhuis Gent, Belgium), David Leonard (Imperial College Healthcare NHS Trust, London, UK), Philip Johnson (Pharmacy Advocacy Director, FASHP, Moffitt Cancer Center, Tampa, Florida, USA), Paul Sessink (President, Exposure Control BV, Wijchen, The Netherlands), Robert McLauchlan (ISOPP Standards Chair, Advisory Panel for MSSA, Austin Health, Melbourne, Australia).

From left, first row:

Tim Whiting (Head, Product and Portfolio Management, BU Oncology Injectables), Hannelore Leitner (Assistant, Portfolio & Product Management, BU Oncology Injectables), Petra Griesenauer (International Medical Marketing Manager, BU Oncology Injectables), Carole Chambers (ISOPP Past President, Tom Baker Cancer Clinic, Calgary, Canada) Rachel White (University Health Network, Toronto, Canada), Shin-ichi Sugiura (Director, JSOPP Japan, Nagoya University Graduate School of Medicine, Nagoya, Japan).

Missing in the picture:

Thomas Connor (National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA), Christoph Koeth (Head of Quality Assurance, BU Oncology Injectables).



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